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PSYCHOTHERAPY DRUGS FOR THE TREATMENT OF MENTAL ILLNESS: PHASE I EVIDENCE OVERVIEW

A REPORT TO THE UTAH PSYCHOTHERAPY DRUG TASK FORCE

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ABBREVIATIONS

5D-ASC	5-Dimension Altered States of Consciousness
5-HT	5-hydroxytryptamine (serotonin)
AE	Adverse event
AUDIT	Alcohol Use Disorders Identification Test
BDI	Beck Depression Inventory
BDNF	Brain-derived neurotrophic factor
BPRS	Brief Psychiatric Rating Scale
CI	Confidence interval
CAPS	Clinician-administered PTSD Scale; CAPS-5 is for the Diagnostic and Statistical Manual of Mental Disorders (DSM) version V, and CAPS-4 is for DSM version IV
COW	Clinical Opiate Withdrawal Scale
CRP	C-reactive protein
DEA	U.S. Drug Enforcement Agency
DMT	*N,N*-dimethyltryptamine
DUDIT	Drug Use Disorders Identification Test
FDA	U.S. Food and Drug Administration
EAT-26	Eating Attitudes Test – 26 item
EQ-5D-3L	EuroQol-5 Dimension-3 Level
fMRI	Function magnetic resonance imaging
GAD-7	Generalized Anxiety Disorder – 7 item
GRID-HAMD	GRID-Hamilton Depression Rating Scale
HADS	Hospital Anxiety and Depression Scale
HADS-D	HADS Depression Subscale
HADS-A	HADS Anxiety Subscale
HAM-A	Hamilton Anxiety Rating Scale
IL	Interleukin
LSAS	Liebowitz Social Anxiety scale
LSD	(D)-Lysergic acid diethylamide
MADRS	Montgomery-Åsberg Depression Rating Scale
MEQ	Mystical Experience Questionnaire
MDD	Major depressive disorder
MDMA	3,4-methylenedioxymethamphetamine
NCT	National Clinical Trial
NEO PI-R	Revised NEO Personality Inventory
OOWS	Objective Opiate Withdrawal Scale
PANAS	Positive and Negative Affect Schedule
POMS	Profile of Mood States
PTGI	Posttraumatic Growth Inventory
PTSD	Post-traumatic stress disorder
RCT	Randomized controlled trial
SD	Standard deviation
SDS	Sheehan Disability Scale
SOWS	Subjective Opiate Withdrawal Scale

SR	Systematic review
STAI	State-Trait Anxiety Inventory
SUD	Substance use disorder
TEAE	Treatment-emergent adverse event
QIDS-SR-16	Quick Inventory of Depressive Symptomatology – Self-Report – 16-item
WSAS	Work and Social Adjustment Scale

1.0 INTRODUCTION

Utah H.B. 167 passed in 2022, creating the "Mental Illness Psychotherapy Drug Task Force" (hereafter referred to as the "Task Force"), a transdisciplinary group of healthcare providers, scientists, lawyers, and patient advocate with the mission to review evidence and provide recommendations on the use of "psychotherapy drugs" to treat mental illness.[1] The **purpose of this report** is to identify evidence to assist the Task Force in performing their "duties" outlined in H.B 167, with an emphasis on efficacy and safety information for psychotherapy drugs when used by people with a mental health disorder.

According to Utah H.B. 167, "psychotherapy drug" is broadly defined as "…a controlled substance that: (a) is not currently available for legal use; and (b) may be able to treat, manage, or alleviate symptoms from mental illness."[1] From this definition, the writers of this report infer psychotherapy drugs to be schedule I controlled substances with clinical studies to support treatment of mental illness. There are over 270 federally-recognized schedule I substances, including opiates, opium-derived products, hallucinogenic compounds, depressants, stimulants, cannabimimetics, and emergency-scheduled substances.[2] Based on interest in hallucinogenic substances for supportive treatment for mental illness,[3] coupled with guidance from content experts, this report will focus on 5 substances with completed or ongoing clinical trials for treatment of mental health conditions. These 5 substances include psilocybin, LSD (D-lysergic acid diethylamide), MDMA (3,4-methylenedioxymethamphetamine), ayahuasca, and ibogaine. We will refer to these substances as the **target psychotherapy drugs.**

Psychedelic drugs are psychoactive substances that are a subtype of hallucinogens.[4] The popularized terms "psychedelic" and "hallucinogen" are often used to refer to a heterogeneous group of compounds that induce mind-altering (eg, changes in perception, thought, mood) effects.[4,5] In most cases, the exact mechanism of the potential therapeutic properties of these compounds is incompletely understood. "Classical psychedelic" substances include psilocybin, LSD, ayahuasca (and its psychoactive component *N,N*-dimethyltryptamine, DMT), among others.[5] The classical psychedelics are agonists or partial agonists at the 5-HT_{2A} receptor,[4] and some additionally act on other receptors.[5] The botanical, ayahuasca, usually contains the psychoactive compound, DMT, and beta-carboline alkaloids, which are monoamine oxidase inhibitors that slow metabolism of DMT.[5] Other hallucinogenic classes considered to have potential psychedelic properties include empathogens or entactogens (eg, MDMA), dissociative anesthetics (eg, ketamine), and atypical hallucinogens (eg, ibogaine).[5] The entactogen MDMA is a laboratory-synthesized phenylethylamine thought to exert its effects through modulation of serotonin, norepinephrine, and dopamine.[6] Ibogaine is a plant-derived indole alkaloid that may have anti-addictive properties; multiple potential mechanisms for this activity have been proposed, including but not limited to N-methyl-D-aspartate (NMDA) antagonism,[7] $\alpha 3\beta 4$ nicotinic receptor antagonism,[5] mu opioid receptor agonism.[5] Refer to **Appendix A** for additional information about the proposed pharmacology of these substances.

Entheogenic substances – psychoactive compounds used in spiritual contexts – have been used for hundreds to thousands of years by cultures around the world. Ayahuasca, psilocybin, and ibogaine are plant-derived entheogenic substances used historically, and currently, as part of religious or ceremonial rites by various cultures.[8] In the US and Western world, despite initial interest in the therapeutic use of classical psychedelics, regulations in the 1960s culminating with the passage of the US Controlled

Substances Act in 1970 and the United Nations Convention on Psychotropic Substances in 1971, restricted access to and research on the psychedelic substances.[5]

Table 1 includes additional background information about the origin, and a brief history regarding the use of the target psychotherapy drugs.

Table 1. Origin and Historical Information about the Target Psychotherapy Drugs

"Classical" psychedelics[a]
LSD (d-lysergic acid diethylamide)
• Synthesized in 1938[5]; plant-alkaloid (ergot)-derived[6] • Marketed as "Delysid" from 1940s-1960s for use with psychotherapy[6] • Studied for psychologic effects (eg, neuroticism, alcoholism; see Rucker et al. 2017[3]) between ~1950s to 1970
Psilocybin (4-phosphoryloxy-N,N-dimethyltrptamine)
• Hepatically converted to psilocin, the primary active compound[5] • Plant-derived: various *Psilocybe* mushrooms[8]; may also be synthesized in the laboratory[9] • Thought to have been used by many people around the world, possibly as early as 9000 BCE[8] • Studied in clinical studies during the 1950s and 1960s, primarily for mystic and subjective effects[5]
Ayahuasca (usually contains **DMT** (N,N-dimethyltryptamine))[5]
• Plant-derived: diverse mixture of various plants; typically containing the vine *Banisteriopsis cappi,* and possibly material from other plants such as *Psychotria viridis, or Diploterys cabrerana*[8] • Harmine-rich *B. cappi* prevents degradation of DMT (contained in *P. viridis* or *D. caberana)* via MAO inhibition[8] • Historically used by people of the Amazon region, and *may* have been used as many as 5,000 years ago[8] • Part of religious ceremonies by the Santo Daime and União Do Vegetal churches[8]
Entactogens/Empathogens[a]
MDMA (3,4-methylenedioxymethamphetamine)
• Synthesized in 1912[6] • Used as a therapeutic tool by some therapists in the 1970s and 1980s until it was classified as a Schedule I controlled substance in 1985[5]
Atypical Hallucinogens[a]
Ibogaine (10-methoxyibogamine)
• Psychoactive 12-hydroxy metabolite[10]: noribogaine[7] • Plant-derived: *Tabernanthe iboga*, a plant native to West Africa[8]; may also be synthesized in a laboratory[11,12] • NIDA-sponsored studies occurred in the early 1990s for addiction, but they were discontinued to due neurotoxicity concerns[5] • Reported therapeutic use by some "clinics" in non-US countries in modern era[8]

Abbreviations: BCE, before the common era; MAO, monoamine oxidase; NIDA, National Institute of Drug Abuse; US, United States of America

Key:

[a] We use these classes of "hallucinogens" for the psychotherapy drugs since they are commonly used in the medical literature.[5] However, some experts may prefer to use other nomenclature.[4]

The decision to make classical psychedelics schedule I controlled substances is usually considered to be socio-politically motivated.[13] Potential safety concerns historically associated with classical psychedelics include psychological or psychiatric risks (eg, abuse potential, psychosis, suicidality, hallucinogenic persisting perception disorder) and physiologic risks (eg, neurotoxicity or cardiovascular toxicity).[14] An overview of toxicity concerns, primarily from compendia including the National Institute on Abuse (NIDA), is shown in **Appendix A**. Note that this compilation may be based on the use of these drugs under widely varying conditions, which may or may not reflect how these drugs have been studied for therapeutic use.

Other US states have considered allowing pathways for the therapeutic use of psilocybin. For example, in 2020, Oregon passed a law granting the authority to develop and provide psilocybin-assisted services.[15] In 2022, a Connecticut workgroup recommended waiting until FDA approval of psilocybin to create state pathways for psilocybin-assisted medical services.[16]

The U.S. Food and Drug Administration (FDA) issued Breakthrough Therapy Designation to MAPS (Multidisciplinary Association for Psychedelic Studies)-sponsored MDMA for the treatment of post-traumatic stress disorder (PTSD),[17] USONA institute-sponsored psilocybin for the treatment of major depressive disorder (MDD),[18] and COMPASS Pathways-sponsored psilocybin for treatment-resistant depression (TRD).[19] This FDA designation is given to drugs showing promise to treat serious illnesses, and creates a smoother pathway to potential FDA approval through FDA-assisted study design, and expedited review of evidence.[20]

2.0 METHODS

To support the Task Force while balancing feasibility, we agreed to a phased approach for reviewing psychotherapy drug evidence. On May 17, 2022, the authors of this report met with Task Force leaders to determine the target psychotherapy drugs, and to prioritize evidence for review. It was agreed that the objective of phase I would be to identify high-level evidence (ie, experimental trials) to determine which mental health conditions, if any, have been rigorously studied with respect to potential therapeutic benefits of psychotherapy drugs. It was also agreed to initially target experimental trials in affected populations (ie, patients diagnosed with a mental health condition). Initially 4 target psychotherapy drugs (MDMA, LSD, psilocybin, ayahuasca) were selected based on the existence of registered phase 2 or higher clinical trials (on clinicaltrials.gov), and input from the content expert. Ibogaine was added as the 5th psychotherapy drug based on feedback from the Task Force at the May 31, 2022 meeting. The agreed plan for phase I was to conduct a literature search for the prioritized evidence, and to summarize these findings as an annotated bibliography.

Following this report of the phase I findings, we may proceed with further evaluation and description of the RCTs identified (ie, phase 2). As there are a variety of studies of the psychotherapy drugs that will not be addressed by the phase I review (eg, research using less robust study designs, or experimental trials in other populations such as healthy volunteers), future work (or phases) may include literature review for these other studies.

Table 2 provides projected phases for reviewing psychotherapy drug evidence. Further details regarding the phase I process are provided in the next section.

Table 2. Overview of Project Phases

Phase	Description	Primary Deliverable(s)
I	Literature search for RCTs in Medline and Embase	• Annotated bibliography • Summary of registered trials on clinicaltrials.gov
II	RCT evidence synthesis, potentially in subphases and, potentially with additional literature searching in other pertinent databases[a] to supplement the phase 1 search	• Summary of RCT efficacy and safety evidence per drug and indication. • Evaluation of the risk-of-bias among RCT evidence
III	To be completed if needed to address questions insufficiently addressed in phase II	

Abbreviations: RCT, randomized controlled trial; TBD, to be determined;

[a] Medline and Embase are large databases that are robust for identifying many relevant studies. Phase II, may involve complementing the initial search with targeted searches in additional databases such as PsycINFO and the Cochrane Central Register of Controlled Trials (CENTRAL).

2.1 Phase I Evidence Review Methods

2.1.1 Clinicaltrials.gov Search Methods

Searches for the target psychotherapy drugs (or related terms) was performed on clinicaltrials.gov. Results were filtered for "interventional studies," and all available data fields were downloaded from clinicaltrials.gov. The search date on clinicaltrials.gov was May 4, 2022 for psilocybin, LSD, ayahuasca or DMT, and MDMA, while clinical trials for ibogaine were searched on June 14, 2022. The search results were manually screened to exclude studies containing healthy volunteers (based on the "conditions" or "title"). Details from the "status", "conditions", and "phases" fields of registered trials in non-healthy volunteers for each psychotherapy drug were collated and summarized for each psychotherapy drug.

2.1.2 Bibliographic Database Search and Screening of Records

Two major bibliographic databases (Ovid-Medline and Embase) were queried for relevant evidence published from 2010 to approximately June 3, 2022. The year 2010 was selected based on feasibility and consultation with content experts familiar with psychotherapy drug clinical trials. An initial search containing free-text and controlled vocabulary terms (ie, MeSH) for the target psychotherapy drugs, and target mental health conditions (together referred to as drug-disease pairs) was developed in Ovid-Medline and translated to Embase. The final literature search for Ovid-Medline was developed by multiple investigators with expertise in conducting literature searches, and internally peer-reviewed. Search terms included synonyms or related terms for each drug and mental health condition. A hedge for randomized controlled trials (RCTs) from The Cochrane Collaboration[21] (sensitivity- and precision-maximized version modified to include "randomised" spelling) was used for the Ovid-Medline search, and a similar RCT-targeted hedge was used for the Embase search.[22] **Appendix B** provides the search strategies used in Ovid-Medline and Embase. In addition to the database searches, we asked Task Force content experts to suggest additional records for screening.

Table 3 shows drug-disease pairs targeted by the literature search. These 5 psychotherapy drugs were selected based on consultation with content experts. The selected target conditions of the drug-disease pairs were informed by a search for registered phase 2 or phase 3 clinical trial(s) on clinicaltrials.gov, and input from content experts.

Table 3. Target Psychotherapy Drug-Disease Pairs Used in the Phase I Literature Search

Psychotherapy Drug[a]	Mental Health Condition(s)[a,b]
MDMA	1. PTSD 2. Anxiety
LSD	1. Anxiety 2. Depression
Psilocybin	1. Anxiety 2. Depression 3. Demoralization associated with chronic illness 4. PTSD 5. Substance Use Disorder
Ayahuasca (or DMT)	1. Depression
Ibogaine	1. Substance Use Disorder

Abbreviations: DMT, *N*,*N*-dimethyltryptamine; LSD, lysergic acid diethylamide; MDMA, 3,4-methylenedioxymethamphetamine; PTSD, post-traumatic stress disorder;

[a] The literature search also contained synonyms or related terms for each drug and disease

[b] Although these specific conditions were used to narrow the search results, trials for other mental health conditions were considered for inclusion for each psychotherapy drug if found among the results.

Title and abstract screening of the literature search results was performed independently and in duplicate using Covidence software. Duplicates were automatically removed by Covidence. Any disagreements during title/abstract screening were resolved by consensus. The full-text of articles voted for possible inclusion by title and abstract review was reviewed by a single investigator, with consultation with other investigators when needed. During title/abstract screening, investigators also "tagged" abstracts of trials of a target psychotherapy drug conducted among healthy volunteers; refer to **Appendix C** for a list of these citations.

In addition to studies meeting criteria for the annotated bibliography, we also saved a list of possible systematic reviews (SRs) or systematic review meta-analyses (SRMAs) of RCTs of the 5 target psychotherapy drugs for a mental health condition. This list of studies included by these reviews will be screened in phase II of this evidence review, and at a minimum, be used to identify any additional relevant trials not captured by our initial search.

2.1.3 Eligibility Criteria for Inclusion in the Annotated Bibliography

Studies included in the annotated bibliography met the following criteria:

- The enrolled study population must include people diagnosed with a mental health condition
- The study intervention(s) must include at least 1 of the 5 psychotherapy drugs (or a metabolite or closely-related congener for one of the drugs) listed in Table 3
- The study included a comparator arm of any type
- The study design was an experimental trial (eg, randomized or nonrandomized allocation), or long-term follow-up of an experimental trial, or a pooled-analysis of experimental trials (eg, a meta-analysis of several similar experimental trials performed by the same investigators) that met other inclusion criteria.
    - Secondary (eg, post-hoc or exploratory) analyses of experimental trials were also included when the exposure for at least part of the analysis remained as the target psychotherapy drug versus comparator were also included for the sake of completeness. Additionally, long-term follow-up studies of experimental trials were included regardless of having a comparator group. **This criterion resulted in including some nonrandomized studies**, which may lack inferential comparisons, or may introduce bias.
- Any outcome or length of follow-up was allowed
- If a study was published as an abstract and/or poster (ie, no full-text available or accessible) and there was insufficient detail to verify that it fully met the annotated bibliography criteria, it was included in our annotations with a notation about the limited information.

Excluded studies or records met one or more of the following criteria:

- Study population was healthy volunteers, without a clearly diagnosed mental health condition, or studies of the psychedelic drug used for recreational or spiritual/religious purpose, where the primary intention was not to clinically evaluate the effects of treatment among people with a psychiatric condition.
- Study lacking a comparator group (eg, single-arm open-label trials)
- Secondary (eg, post-hoc, exploratory, subgroup) analyses of an experimental trial lacking an analysis that maintained the randomized groups
- Abstracts that were duplicates of a study published in full-text
- Narrative review articles (ie, reviews lacking systematic review methods)
- Duplicative records pushed to full-text review to ensure that a trial or trial detail was not missed (ie, published protocols, or erratum)

2.1.4 Annotated Bibliography

An annotated bibliography of included studies was created using Endnote (Endnote X9, Clarivate Analytics). The annotated bibliography includes a brief description of the studied population, psychotherapy drug intervention, comparator, primary outcome measure and/or the outcome included in the abstract if a primary outcome was not specified, study design, primary conclusion(s), and limitations. When possible, for feasibility, extracted conclusions was limited to information reported in the abstract. Limitations were those reported by the study authors in the discussion section, with occasional additional limitations added as per the evidence review investigator.

Characteristics of studies included in the annotated bibliography were summarized using descriptive statistics.

3.0 RESULTS

3.1 Clinical Trials for Mental Health Conditions Registered on Clinicaltrials.gov

A list of registered trials for each psychotherapy drug was downloaded from clinicaltrials.gov to provide an overview of mental health conditions under study for each psychotherapy drug. Note that this trial list is from a single database of registered trials, which may not contain all studies outside of the US.

According to the information from clinicaltrials.gov, the psychotherapy drug furthest along in the clinical development process, having at least 1 completed phase 3 study, is MDMA for treatment of PTSD (NCT03537014).[23] There are 2 additional registered phase 3 trials of MDMA for PTSD that are reported as recruiting (NCT04077437)[24] or enrolling (NCT04714359, an extension study).[25] Other drug-disease pairs next furthest along in clinical development with at least 1 or more *completed* phase 2 trial(s) include LSD for illness-related anxiety[26,27]; MDMA for cancer-associated anxiety[28] and social anxiety disorder[29]; and psilocybin for treatment-resistant depression,[30,31] major depressive disorder,[32,33] and cancer-associated psychological distress (eg, anxiety and depressive symptoms).[34]

3.1.1 Clinical Trials for LSD

Table 4 provides the number, phase, and status of registered clinical trials (on clinicaltrials.gov) for LSD by mental health condition.

Table 4. LSD Registered Clinical Trials for Mental Health Indications[35]

Indication[a]	Number of Trials	Trial Phase	Status
Illness-related Anxiety	2	*Phase 2*	**Completed**
MDD	1	*Phase 2*	Recruiting

Abbreviations: LSD, lysergic acid diethylamide; MDD, major depressive disorder

[a] There is also a registered phase 2 trial for *cluster headache* that is recruiting[36]

3.1.2 Clinical Trials for MDMA

Table 5 provides the number, phase, and status of registered clinical trials (on clinicaltrials.gov) for MDMA by mental health condition.

Table 5. MDMA Registered Clinical Trials for Mental Health Indications[37]

Indication[a]	Number of Trials	*Trial Phase* (number of trials)	Status (number of trials)
Alcohol Use Disorder	1	*Phase 1*	Unknown
Amphetamine-related Disorders	1	*Phase 1*	**Completed**
Autism Spectrum Disorder	1	*"Early Phase 1"*	**Completed**
Cancer-associated Anxiety	2	*Phase 2*	**Completed** (1); terminated (1)
Eating Disorders (anorexia or	1	2	Pre-recruitment

Table 5. MDMA Registered Clinical Trials for Mental Health Indications[37]

Indication[a]	Number of Trials	*Trial Phase* (number of trials)	Status (number of trials)
binge-eating)			
PTSD	21	*Phase 1 or 1/2* (2); *Phase 2* (16); *Phase 3* (3)	**Completed (10)[b]**; Recruiting/Enrolling (7); Pre-recruitment (1); Terminated (2); Withdrawn (1)
Post-partum PTSD with Opioid Use Disorder	1	*Phase 2*	Pre-recruitment
Social Anxiety Disorder[c]	2	*Phase 2*	**Completed (1);** Recruiting (1)

Abbreviations: PD, pharmacodynamic; PK, pharmacokinetic; PTSD, post-traumatic stress disorder

[a] Other trials list *substance-related disorders* in general (PK/PD focused),[38-44] *social cognition/social interactions,*[45-47] *startle response,*[48] and *diabetes insipidus* (measuring oxytocin changes)[49]

[b] One phase 3 PTSD trial completed[23]; others are recruiting or enrolling[24,25]

[c] Includes 1 trial for social anxiety in adults with autism spectrum disorder[29]

3.1.3 Clinical Trials for Ayahuasca

Table 6 provides the number, phase, and status of registered clinical trials (on clinicaltrials.gov) for ayahuasca by mental health condition.

Table 6. Ayahuasca Registered Clinical Trials for Mental Health Indications[50]

Indication[a]	Number of Trials	*Trial Phase* (number of trials)	Status (number of trials)
MDD	3	*Phase 1* (1); *Phase 1/2:* (2)	**Completed (1)[b];** Recruiting (1); Pre-recruitment (1)

Abbreviations: MDD, major depressive disorder;

[a] Another early phase 1 trial examines *emotions/social empathy/cognition*[51]

[b] One phase 1/2 trial completed[52]

3.1.4 Clinical Trials for Psilocybin

Table 7 provides the number, phase, and status of registered clinical trials (on clinicaltrials.gov) for psilocybin by mental health condition.

Table 7. Psilocybin Registered Clinical Trials for Mental Health Indications[53]

Indication[a]	Number of Trials	*Trial Phase* (number of trials)	Status (number of trials)
Substance Use Disorders			
Alcohol Use Disorder	5	*Phase* 2	Active (2); Pre-recruitment (1); Recruiting (1); Unknown (1)
Cocaine-related Disorders	1	*Phase* 2	Recruiting
Methamphetamine Use Disorder	2	*Phase 1 (1); Phase 2* (1)	Pre-recruitment
Nicotine Dependence	1	N/A	Recruiting
Depression, Anxiety, Trauma, or Psychological Distress Associated with Other Illness			
Alzheimer's Disease-Associated Depression	1	"Early Phase 1"	Recruiting
Cancer-Associated Anxiety	4	*Phase 1* (1); *Phase 1/2* (1); *Phase 2* (2)	**Completed (3)[b];** Withdrawn (1)
Cancer-Associated Psychological Distress	2	*Phase* 1	Pre-recruitment (1); Recruiting (1)
Chronic-disease Associated Trauma	1	*Phase* 1	Pre-recruitment
Palliative-care Associated Existential Distress	1	*Phase* 1/2	Pre-recruitment
Parkinson's Disease Associated Depression or Anxiety	1	*Phase* 2	Recruiting
Depressive Disorders			
Bipolar II Disorder[c]	1	*Phase* 2	Recruiting
Dysthymia	1	*Phase* 2	Pre-recruitment
Major Depressive Disorder	9	*Phase 1* (2); *Phase 2* (7)	Active (4); **Completed (2)[d];** Pre-recruitment (1); Recruitment (1); Unknown (1)
MDD with Alcohol Use Disorder	1	*Phase* 2	Recruiting
Persistent Anxiety and/or Depression	1	*Phase* 2	Pre-recruitment
Treatment-Resistant Depression[c]	8	*Phase* 2	Active (1); **Completed (2);** Recruiting (5)
Other Mental Health			
Anorexia Nervosa	3	*Phase 1* (1); *Phase 1/2* (2); *Phase 2* (1)	Active (1); Recruiting (2)
Binge Eating Disorder	1	*Phase* 2	Recruiting
Body Dysmorphic Disorder	1	*Phase* 2	Active
Clinician Burnout	1	*Phase* 1/2	Recruiting
Demoralization[e]	3	*Phase 1* (2); *Phase 2* (1)	**Completed (1)[e];** Pre-recruitment (1); Recruiting (1)

Table 7. Psilocybin Registered Clinical Trials for Mental Health Indications[53]

Indication[a]	Number of Trials	*Trial Phase* (number of trials)	Status (number of trials)
Obsessive-compulsive Disorder	3	*Phase 1* (2); *Phase 1/2* (1)	Pre-recruitment (1); Recruiting (2)
Perception Disorders	2	*Phase* 1	Pre-recruitment (1); Recruiting (1)
PTSD[f]	2	*Phase* 2	Pre-recruitment (1); Recruiting (1)

Abbreviations: AIDS, acquired immunodeficiency syndrome; N/A, not applicable; PTSD, post-traumatic stress disorder

[a] Other indications include *pain disorders* (ie, chronic low back pain, fibromyalgia, phantom limb pain)[54-57]; *headache disorders* (ie, cluster, migraine, concussion-associated headache, short neuralgiform headache)[58-62]; *post-treatment Lyme Disease*[63]; and *religious or spiritual problems*[64]

[b] Includes one completed phase 2 trial for anxiety and depressive symptoms among people with cancer[34]

[c] One treatment-resistant depression trial is for people with bipolar II disorder.[65] The other bipolar II disorder trial lists many symptoms (depression and others) associated with bipolar disorder as outcomes.[66]

[d] Includes 2 completed phase 2 trials for major depressive disorder (one of these being a proof of concept trial)[30,31]

[e] Includes 1 trial for end-of-life demoralization.[67] The completed trial is a phase I trial among people with long-term AIDS.[68]

[f] Includes 1 trial for treatment-resistant PTSD[69]

3.1.5 Clinical Trials for Ibogaine

Table 8 provides the number, phase, and status of registered clinical trials (on clinicaltrials.gov) for ibogaine by mental health condition.

Table 8. Ibogaine Registered Clinical Trials for Mental Health Indications[70]

Indication	Number of Trials	Trial Phase	Status
Opioid withdrawal/ opioid dependence[a]	2	*Phase 1/2:* (1); Phase 2 (1)	Recruiting (2)
Alcohol use disorder	1	2	Pre-recruitment

[a] Both trials are for medically-supervised withdrawal from opioids, including withdrawal from methadone

3.2 Annotated Bibliography

3.2.1 Bibliographic Database Search Results

Our literature search in Ovid-Medline and Embase retrieved 928 records. An additional 5 records (posters from a grey literature source) were screened. Refer to **Appendix D** for the PRISMA diagram showing the identification of included studies. Covidence software or manual screening removed 201

duplicate records, and after screening titles and abstracts, 604 records did not meet our eligibility criteria for the annotated bibliography. After screening the full-texts (including references only available as a poster or abstract), 33 references were considered irrelevant for the reasons shown in **Figure D1**. The most common reasons for exclusion were duplicate abstract (meaning that we already included the full-text, or it is a duplicate of another abstract), healthy volunteer population only (wrong population), and studies without a comparator. A list of studies excluded during full-text review organized by a reason for exclusion is included in **Appendix E.** Overall, 43 unique references met criteria for inclusion in the annotated bibliography.

Citations for studies that may have included psychotherapy drug clinical trials of healthy volunteers based on the title and/or abstract are listed in **Appendix C.**

3.2.2 Overview of the Annotated Bibliography

The annotated bibliography describes the population (P), intervention (I), comparator (C), outcome (O), time of measurement of the outcome (T), and study design (S) of included studies. When reported, the National Clinical Trial (NCT) number was included. Additionally, **study results, primarily based on information in the study abstract, and limitations, primarily based on those reported by the study authors are described. Study design was primarily based on author report; in some cases, authors described studies experimental trials, but they may not be truly experimental.** The annotated bibliography is organized by psychotherapy drug and treated condition. Where possible, articles derived from the same trial (ie, reporting the same NCT number or inferred to be from the same trial) are listed together.

There are 43 references (citations) in the annotated bibliography. The majority of citations are for MDMA (n=18, 41.9%), followed by psilocybin (n=16, 37.2%). Many studies have been used to publish more than one reference. There are 7 unique trials for MDMA and psilocybin, 2 for LSD, and 1 each for ayahuasca and ibogaine. Studies that authors self-reported as long-term follow-up of experimental trials are (n = 5, 11.6%) of the identified citations. Many of the trials are relatively small; the median number of enrolled participants, calculated using unique trials only, is 23 for MDMA, 44 for psilocybin, and 15.5 for LSD. For ayahuasca and ibogaine, only 1 unique trial was identified; the number enrolled participants was 35 and 57, respectively. The unique trials included multiple types of comparators to the psychotherapy drug including an active comparator (an antidepressant, escitalopram) in 1 trial, active placebo, inert placebo, patients on a waitlist that did not receive treatment at the time of the psychotherapy drug. The most common comparator was active placebo; in most cases, this was a low-dose of the psychotherapy drug that was considered by the investigators to be lacking appreciable therapeutic activity. Other active placebos were medications with overlapping side effects with the psychotherapy drug, but that were not expected to be effective therapeutics for the mental health condition (eg, niacin, or zinc). In most cases, both treatment groups received psychological support or psychotherapy in addition to the drug.

The studied mental health condition among included references varied by psychotherapy drug. For MDMA, the most common is PTSD (n = 5 trials; 71.4 of unique MDMA trials), and for psilocybin it is major depressive disorder (n = 3 trials; 42.9% of unique psilocybin trials) and psychological distress (eg, depression, anxiety) associated with cancer (n = 3 trials; 42.9% of unique psilocybin trials) For LSD, ayahuasca, and ibogaine, included references are for 1 condition each: anxiety associated with life-

threatening illness, major depressive disorder, and management of withdrawal in people receiving opioid substitution therapy, respectively. Regarding efficacy outcomes,[†] many studies assessed changes in symptoms for the studied mental health condition based on a rating scale (eg, change in depression symptoms among people with major depressive disorder). Various scales/questionnaires were used for each condition. For depression, these include HADS-D, GRID-HAMD, HAMD, BDI, QIDS-SR-16, and MADRS. Suicidality was assessed via specific questions on depression, or other psychiatric questionnaires (eg, BPRS, desire to hasten death on a demoralization scale). Variable questionnaires were also used to assess changes in types of anxiety, including HADS-A, STAI, GAD-7, and HAM-A. PTSD symptoms were primarily assessed using variations of the CAPS (eg, CAPS-4, CAPS-5, and German language CAPS). Posttraumatic growth was also assessed in 1 trial (using the PTGI). Some studies of people with PTSD assessed common comorbid symptoms including eating disorders (EAT-26), alcohol or substance use (AUDIT, DUDIT), and sleep quality (PSQI). Other types of outcomes or scales used include fMRI imaging (eg, for functional connectivity), magnetic resonance spectroscopy imaging, altered cognition (eg, cognitive flexibility via PCET or DSST), altered consciousness (eg, 5D-ASC), changes in mood or affect (eg, POMS, PANAS), disability (SDS) or quality of life (eg, EQ-5D-3L), changes in biomarkers, and incidence of adverse events.

The length of follow-up[‡] for most studies was relatively short: for MDMA the range was 1 month to 74.3 months; for psilocybin it was 8 hours to 4.5 years (mean duration for the cohort); and for LSD it was 3 months to 12 months. For ayahuasca, the only unique trial included follow-up of 48 hours to 7 days; and for ibogaine, the primary outcome was measured at 216 hours. The time to outcome assessment was not reported by all studies.

Table 9 summarizes characteristics of studies in the annotated bibliography

[†] Our focus was primarily outcomes reported in the study abstract. Thus, this list of outcomes may not be comprehensive. **See the abbreviations list at the start of this report for definitions of scale abbreviations.**
[‡] Length of follow-up is primarily for outcomes reported in the study's abstract. How time to outcome was calculated varied by study (eg, some used time from baseline, and others used time since drug administration). The length summarized here reflects how the studies reported it.

Table 9. Overview of Studies Included in the Annotated Bibliography

Description	Psychotherapy Drug Studied				
	MDMA	**Psilocybin**	**LSD**	**Ayahuasca**	**Ibogaine**
Number of unique trials[a]	7	7	2	1	1
Number of citations (% of total citations)	18 (41.9%)	16 (37.2%)	3 (7.0%)	5 (11.6%)	1 (2.3%)
Additional Citation Study Types (% of citations per drug[b])					
Long-term follow-up of an experimental trial[c]	2 (11.1%)	2 (12.5)	1 (33.3%)	--	--
Pooled meta-analysis of clinical trials	4 (22.2%)	--	--	--	--
Unknown from abstract	1 (5.6%)	--	1 (33.3%)	--	--
Citations with reported NCT(s) (n, % of citations per drug)	14 (77.8%)	13 (81.3%)	2 (66.6%)	5 (100%)	--
Median number of randomized participants, per unique trials (range, minimum to maximum)	23 (12 to 90)	44 (12 to 233)	15.5 (12 to 19)	N/A, *n* for 1 trial = 35	N/A, *n* for 1 trial = 57
Comparator type[d] (n, % of unique trials per drug[e])					
Active	--	1 (14.3%)	--	--	--
Active placebo	4 (57.1%)	5 (71.4%)	1 (33.3%)	1 (100%)	--
Placebo	3 (42.8%)	--	--	--	1 (100%)
Other (ie, waitlisted patients)	--	1 (14.3%)	--	--	--
Mental Health Condition (n, % of unique trials per drug[e])					
Alcohol use disorder	--	1[f] (14.3%)	--	--	--
Anxiety associated with life-threatening illness	--	--	3 (100%)	--	--
Autistic adults with social anxiety disorder	1 (14.3%)	--	--	--	--
Cancer-associated anxiety, depression, and/or psychological distress	1 (14.3%)	3 (42.9%)	--	--	--
Major depressive disorder	--	3 (42.9%)	--	5 (100%)	--

Table 9. Overview of Studies Included in the Annotated Bibliography

Description	Psychotherapy Drug Studied				
	MDMA	**Psilocybin**	**LSD**	**Ayahuasca**	**Ibogaine**
People receiving opioid-substitution therapy	--	--	--	--	1 (100%)
PTSD	5 (71.4%)	--	--	--	--

Abbreviations: n, number; NCT, National Clinical Trial; PTSD, post-traumatic stress disorder;

Key:

[a] There are multiple publications resulting from a single study. This is an *approximate number* based on publications that are most likely from the same trial (eg, based on shared NCT number, or other information reported by the investigators). For MDMA, studies only reported as part of a meta-analysis are not counted as a unique trial.

[b] The percentage was calculated using the total number of citations for that psychotherapy drug as the denominator

[c] This group is for references that self-identified as long-term follow-up of experimental trials.

[d] Active comparator refers to drug interventions expected to be effective for improving the primary efficacy outcome (eg, antidepressant for depression symptoms). "Active placebo" refers to comparators that were a low dose of the psychotherapy drug considered to be minimally efficacious, or comparators that are not active for treating the studied condition (eg, niacin). Placebo is an inert substance. Most trials studied the drug interventions in combination with psychological support and/or psychotherapy.

[e] The percentage was calculated using the number of unique trials for a given psychotherapy drug as the denominator

[f] The study of psilocybin for alcohol use disorder is limited to a preliminary descriptive analysis of an ongoing trial.

3.2.3 MDMA Studies

3.2.3.1 MDMA for PTSD

3.2.3.1.1 Citations addressing the original phase 3 trial by Mitchell et al. 2021 (NCT03537014)

1. **Mitchell JM, Bogenschutz M, Lilienstein A, et al. MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. *Nat Med.* 2021;27(6):1025-1033.**
   P: Adults (mean age of 41 years, 65.6% female at birth) with severe (Clinician-Administered PTSD Scale [CAPS]-5 total score ≥ 35; mean score of 44.1 at baseline) PTSD. Other psychiatric medications were discontinued before baseline (total n randomized = 91)
   I: MDMA (80-180 mg in divided doses [first dose at start of treatment session, plus half-dose 1.5 to 2.5 hours later] *three times,* during treatment sessions) plus "manualized" therapy by trained therapists with a master's or higher degree (3, 90-minute 'preparatory' sessions pre-treatment plus 3, 8-hour treatment sessions, separated by ~4 weeks plus 3, 90-minute integration' sessions following each treatment session and separated by about 1 week)
   C: Inert placebo in divided doses with "manualized" therapy, both as per the MDMA arm
   O: Change from baseline in the CAPS-5 PTSD severity total score. The secondary endpoint was functional impairment per the Sheehan Disability Scale (SDS).
   T: Primary outcome, and secondary endpoint measured at baseline and 18 weeks (~8 weeks after last therapy treatment session).
   S: Phase 3, randomized (1:1), double-blind (participants + staff + verification of outcome by independent rater), multi-site (US, Canada, Israel), placebo-controlled trial
   Primary conclusion(s): Significant improvement in CAPS-5 total severity score between baseline and the third therapy session (18 weeks later) for the MDMA arm versus placebo arm (mean change [SD]: MDMA, –24.4 [11.6] vs placebo, –13.9 [11.5]; between-group difference: 11.9, 95% CI 6.3 to 17.4, P<0.0001; effect size, *Cohen's d* = 0.91). SDS total scores were also significantly reduced from baseline to 2 months post-treatment for MDMA-treated participants compared to placebo-treated participants (mean change [SD]: MDMA, –3.1 [2.6] vs placebo, –2.0 [2.4]); P for between-group difference = 0.0116, *d* = 0.43). MDMA appeared safe, with either similar or fewer treatment-emergent events of suicidality, abuse, or QT interval prolongation compared to placebo.
   Limitations (per authors): Enrolled smaller size than planned, though still met sample size for power calculation; minimal racial/ethnic diversity of participants; short follow-up; safety reported by therapists, which could have compromised blinding; blinding was challenging, and may have been compromised for some participants.

2. **Brewerton TD, Wang JB, Lafrance A, et al. MDMA-assisted therapy significantly reduces eating disorder symptoms in a randomized placebo-controlled trial of adults with severe PTSD. *J Psychiatr Res.* 2022;149:128-135.**
   P: Adults with severe PTSD without an active purging eating disorder (n = 89 participants; 82 completers); at baseline, 15% of participants had clinically elevated EAT (Eating Attitudes Test)-26 scores, and an additional 31.5% were classified as "at-risk"
   I/C: Refer to Mitchell et al. 2021
   O: Between-group change in baseline-adjusted EAT (Eating Attitudes Test)-26 self-reported questionnaire scores
   T: Time to follow-up EAT-26 measurement *not reported*, measured at end of study (visit 20)

S: *Exploratory analysis* of a pre-specified measurement from the randomized, double-blind, placebo-controlled phase 3 trial (refer to Mitchell et al. 2021)

Primary conclusion(s): Among participants finishing the trial, a significantly larger decrease in EAT-26 score from baseline to follow-up was observed in the MDMA-treated arm versus PBO arm (mean change [SD]: MDMA, –3.04 [6.24] vs placebo, –0.68 [8.04]; P = 0.0335 for between group difference; effect size [*Hedges g]* = 0.33).

Limitations (per authors): Analysis was only performed on participants with full data, including only those completing the trial, which may introduce bias; small sample size for subgroup analysis; post-treatment BMI was not collected for the full study sample

3. **Nicholas CR, Wang JB, Coker A, et al. The effects of MDMA-assisted therapy on alcohol and substance use in a phase 3 trial for treatment of severe PTSD. *Drug Alcohol Depend.* 2022;233:109356.**

P: Adults with severe PTSD. Mild or moderate (in early remission) alcohol or cannabis use disorders were allowed, but other substance use disorders (SUD) within the prior 12 months were excluded (n = 89 participants; 82 completers); at baseline, ~25% of participants had a history of alcohol use disorder and 17% had a history of a SUD.

I/C: Refer to Mitchell et al. 2021

O: Change in alcohol use disorder identification test (AUDIT) and drug use disorder identification test (DUDIT) self-reported measures between baseline and study completion

T: Time to follow-up AUDIT/DUDIT measurement not reported, measured at end of study

S: *Exploratory* analysis from the randomized, double-blind, placebo-controlled phase 3 trial

Primary conclusion(s): Among finishers of the trial, a significantly larger decrease in AUDIT score from baseline to follow-up was observed in the MDMA-treated arm versus placebo arm (mean change [SD]: MDMA, –1.02 (3.52 versus placebo, 0.40 (2.70); P= 0.0536 for between group difference; effect size [*Hedges g*]= 0.45). No significant difference in change in DUDIT score between treatment arms was observed.

Limitations (per authors): Participants lacked severe alcohol use disorder, and any type of other substance use disorder (other than cannabis) at baseline.

3.2.3.1.2 Citations addressing the original phase 2 trial: Mithoefer et al. 2018 (NCT01211405)

4. **Mithoefer MC, Mithoefer AT, Feduccia AA, et al. 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for post-traumatic stress disorder in military veterans, firefighters, and police officers: a randomised, double-blind, dose-response, phase 2 clinical trial. *Lancet Psychiatry.* 2018;5(6):486-497.**

P: Adults with moderate-severe chronic PTSD (CAPS-IV score ≥ 50; mean baseline score of ~82 to 89) with trauma from serving in wars, or as a firefighter or police officer. Participants must have failed or not tolerated prior treatments, and psychotropic medication other than sedative/hypnotics or as-needed anxiolytics used outside of drug sessions (total n randomized = 26)

I: *During blinded trial period:* MDMA [(75 mg or 125 mg given as an initial dose plus optional supplemental dose 1.5 to 2 hours later) *two times,* during treatment sessions] plus therapy by a male and female therapist co-team (3, 90-min 'preparatory' sessions pre-treatment plus two 8-hour treatment sessions, separated by ~4 weeks plus two 'integration' sessions following each treatment session and separated by about 1 week). *During the unmasked crossover follow-up period:* MDMA 125 mg plus co-team led therapy (1 treatment session plus 3 'integration' sessions)

C: *During blinded trial period:* active control (low-dose MDMA, 30 mg) plus therapy, as per the MDMA intervention groups. *During the unmasked crossover follow-up period* (crossover of people receiving MDMA 30-75 mg in the blinded period): MDMA 100-125 mg plus co-team led therapy (1 'preparatory' sessions + 3 treatment session about 4 weeks apart + 3 'integration' sessions)

O: Mean change in CAPS-4 total score

T: Primary *blinded* outcome measured between baseline and ~4 weeks after the last therapy treatment session. *During the unmasked crossover period:* 2-month follow-up after 3rd MDMA treatment session, and a 12-month follow-up (12 months after last 100-125 mg MDMA dose)

S: Phase 2, randomized (1 MDMA 30 mg: 1 MDMA 75 mg: 2 MDMA 125 mg), double-blind (participants + investigators + outcome verification by independent rater), single-site (US outpatient clinic) trial. After the time of the primary outcome measurement, there was a crossover, unmasked follow-up period.

Primary conclusion(s): Significant reductions in mean CAPS-IV score between baseline and 4 weeks after the second MDMA treatment session were observed for both MDMA intervention groups compared to the low-dose (30 mg) (mean change [SD]: MDMA 125 mg, –58.3 [9.8] versus MDMA 75 mg, –44.3 [28.7] and MDMA 30 mg, –11.4 [12.7]; P=0.001 for comparison to 30 mg). During the crossover period, the group initially receiving 75 mg failed to show a significant decrease in PTSD symptoms after receiving 100-125 mg; however, the group initially receiving 30 mg demonstrated significant decreases after receipt of the higher MDMA dose. PTSD symptoms were significantly reduced at the 12-month follow-up relative to baseline for all study arms. Treatment-emergent adverse events (AE) were report by 20 patients (85 total events, 4 considered serious). One serious AE ("an acute increase in premature ventricular contractions"[71] in a patient with a history of this condition) was considered possibly drug-related; the affected patient recovered and lacked evidence of lasting damage.

Limitations (per authors): Small sample size that included primarily white men; possibly compromised blinding; the 12-month follow-up is limited by the lack of a comparison group that did not receive higher-dose MDMA (125 mg).

5. **Barone W, Beck J, Mitsunaga-Whitten M, Perl P. Perceived Benefits of MDMA-Assisted Psychotherapy beyond Symptom Reduction: Qualitative Follow-Up Study of a Clinical Trial for Individuals with Treatment-Resistant PTSD. *J Psychoactive Drugs.* 2019;51(2):199-208.**

***NCT not reported**, but described as follow-up to the Mithoefer et al. 2018 study*

P: Adults with moderate-severe treatment-resistant PTSD with trauma from serving in wars, or as a firefighter or police officer (total n randomized = 26; participants in follow-up sample = 19)

I/C: Refer to Mithoefer et al. 2018. At the time of follow-up all participants had received MDMA-assisted therapy.

O: Themes via interpretative phenomenological analysis of participant semi-structured interviews

T: Twelve month follow-up after trial completion

S: *Retrospective* qualitative follow-up study of a phase 2, randomized, double-blind trial

Primary conclusion(s): "All participants reported experiencing lasting personal benefits and enhanced quality of life that extend beyond quantifiable symptom reduction"[72]

Limitations (per authors): Retrospectively-designed study (limited to available recorded interviews from the trial follow-up); information available for 19 of 26 trial participants; interviews were originally conducted by one of the study therapists with established patient rapport; generalizability to people other than white males.

3.2.3.1.3 Citations addressing the original phase 2 trial: Ot'alora et al. 2018 (NCT01793610)

6. **Ot'alora GM, Grigsby J, Poulter B, et al. 3,4-Methylenedioxymethamphetamine-assisted psychotherapy for treatment of chronic posttraumatic stress disorder: A randomized phase 2 controlled trial. *J Psychopharmacol.* 2018;32(12):1295-1307.**

P: Adult with moderate-severe (CAPS-IV score ≥ 50) chronic PTSD that failed to response to at least 1 regimen of psychotherapy or drug treatment (total n randomized = 28)

I: *During blinded trial period*: MDMA [(100 or 125 mg initial dose + optional supplemental dose 1.5 hours later) two times, during treatment sessions] plus therapy (three 90-min 'preparatory' sessions pre-treatment plus two, 8-hour treatment sessions, separated by ~1 month plus 3 'integration' sessions following each treatment session 1 week apart, including daily phone contact after 1st integration session). *During the unmasked crossover follow-up period*: MDMA 100-125 mg plus co-team led therapy (1 treatment session + 3 'integration' sessions)

C: *During blinded trial period*: active control (low-dose MDMA, 40 mg) plus therapy matching the MDMA intervention groups. *During the unmasked crossover follow-up period* (crossover of people receiving MDMA 40 mg in the blinded period): MDMA 100-125 mg plus co-team led therapy (1 'preparatory' session + 2 treatment sessions about 1 month apart + 3 'integration' sessions; followed by 1 treatment session + 3 'integration' sessions after the endpoint measurement post 2 treatment sessions)

O: Mean change in CAPS-4 total score

T: Primary blinded outcome measured between baseline and ~1 month after the last therapy treatment session (2 treatment sessions). During the unmasked crossover period: 2-month follow-up after 3rd MDMA treatment session, and a 12-month follow-up (12 months after last 100-125 mg MDMA dose)

S: Phase 2, randomized(~2 MDMA 125 mg: 1.5 MDMA 100mg: 1 MDMA 40 mg), double-blind (participants + investigators + outcome verification by independent rater) dose-finding, single site (US outpatient clinic) trial. After the time of the primary outcome measurement, there was a crossover, unmasked trial follow-up period.

Primary conclusion(s): Numerically larger decreases in PTSD symptom severity from baseline to 1 month after 2 MDMA sessions were observed in the intention-to-treat analysis of the MDMA 125 mg arm (mean change [SD]: –26.3 [29.5]) and MDMA 100 mg arm (mean change [SD]: –24.4 [24.2]) compared to the MDMA 40 mg arm (mean change [SD]: –11.5 [21.2]); the difference compared to the low-dose arm was statistically significant by per-protocol analysis. Significant improvements in PSTD symptoms relative to baseline were detected at 12 months. Authors report a lack of serious AE attributable to MDMA.

Limitations (per authors): Small sample size that included primarily white women; possibly compromised blinding; at the 12 month follow-up, there was not a comparison group and participants were aware of initial group assignments.

3.2.3.1.4 Citations addressing the original phase 2 trial: Oehen et al. 2013 (NCT00353938)

7. **Oehen P, Traber R, Widmer V, Schnyder U. A randomized, controlled pilot study of MDMA (+/-3,4-Methylenedioxymethamphetamine)-assisted psychotherapy for treatment of resistant, chronic Post-Traumatic Stress Disorder (PTSD). *Journal of psychopharmacology.* 2013;27(1):40-52.**

This study secondarily aimed to confirm findings from Mithoefer et al. 2011 in a new setting.

P: Adults (mean age = 41.4) with treatment-resistant PTSD (CAPS score ≥ 50 with a history of ≥ 6 months of psychotherapy as well as 3 months of treatment with an SSRI). Total n randomized = 14; total n included in analysis = 12 (2 additional patients were randomized but discontinued participation after the first MDMA treatment session).

I: Three full-dose MDMA administrations sessions, each consisting of 125 mg MDMA followed by another 62.5 mg MDMA dose administered 2.5 hours later during full-day psychotherapy sessions. In addition, 12 non-drug psychotherapy sessions were performed.

C: Three low-dose MDMA administration sessions, each consisting of 25 mg of MDMA followed up by another 12.5 mg MDMA dose administered 2.5 hours later during full-day psychotherapy sessions and an additional 12 non-drug psychotherapy sessions. Considered to be an "active placebo" at low doses that are not expected to produce significant applicable effects.

O: Change in mean CAPS score

T: CAPS scores measured at baseline, 3 weeks after MDMA session 2, 3 weeks after MDMA session 3, and 2 months, 6 months, and 12 months after MDMA sessions 3. Referred to as T0-T5, respectively.

S: Phase 2, double-blinded, randomized (2:1), "active placebo" controlled experimental trial in German-speaking Switzerland. The masked period was followed by an open-label cross-over period where "active placebo" participants received full-dose MDMA (3 MDMA sessions plus 12 non-MDMA therapy sessions), and high-dose MDMA non-responders optionally received additional higher-dose MDMA (150 mg plus supplemental 75 mg during 2 sessions with 7 non-drug therapy sessions).

Primary Conclusions: Lack of statistically significant improvement in mean CAPS score from baseline to 3 weeks after MDMA session 3 (end of blinded period) for the full-dose versus active placebo comparison (mean CAPS score change from T0 to T2 [SD]: full-dose MDMA, –15.6 (18.1) versus low-dose active placebo, –3.2 CAPS [15.3]; P=0.066]. Statistically significant improvement in secondary outcome of posttraumatic diagnostic scale (PDS) score for high-dose MDMA treated participants vs active-placebo treated patients from T0 to T2 occurred (P=0.014). Authors deny any serious MDMA-related AE.

Limitations (per authors): Small sample size that was underpowered for safety outcomes and likely unreliable for efficacy outcomes; generalizability concerns based on population of primarily female Europeans; 2:1 ratio of intervention: control assignment; possibility of unmasking during the blinded period; some patients in the low-dose MDMA control group exhibited a higher than expected response to the supposedly inactive dose; therapy adherence was assessed in a post-hoc analysis (not reported) and some protocol deviations favoring increased directiveness of therapy occurred.

3.2.3.1.5 Pooled analyses from multiple phase 2 trials

8. **Ponte L, Jerome L, Hamilton S, et al. Sleep Quality Improvements After MDMA-Assisted Psychotherapy for the Treatment of Posttraumatic Stress Disorder. *J Trauma Stress.* 2021;34(4):851-863.**

    NCT01958593, NCT01211405, NCT01689740, NCT01793610 (trial IDs: MP-8 [US], MP-12 [US], MP-4 [Canada], MP-9 [Israel])

    P: Adults with moderate-severe PTSD (CAPS-4 score ≥ 50 or ≥ 60 in 1 trial) [total n randomized = 68; 62 with complete data]

    I: *Varied by trial;* active-dose MDMA (75-125 mg)-assisted therapy (2 blinded; 1 open-label); see phase 2 trial descriptions for examples of the regimens

    C: *Varied by trial;* control-dose MDMA (0-40 mg)-assisted therapy (2 blinded); see phase 2 trial descriptions for examples of the regimens

O: Change in sleep quality based on the Pittsburgh Sleep Quality Index (PSQI) self-reported questionnaire

T: Blinded measurements were made 1 month after the 2nd MDMA/placebo-assisted therapy session; additional open-label follow-up occurred: treatment-end, occurring 2 months after the 3rd therapy session for the active-MDMA arm and control-MDMA arm, and a 12-month follow-up, occurring 12 months after the final open-label MDMA therapy session.

S: *Exploratory* pooled secondary analysis of 4 phase 2, placebo-controlled, randomized trials. These trials included an initial blinded, parallel group period followed by an open-label cross-over period when participants that initially received control-dose MDMA switched to receive active MDMA treatment. During the open-label period, the active-MDMA group completed 1 additional MDMA-therapy session, and the control-MDMA arm completed 3 MDMA-assisted therapy sessions.

Primary conclusion(s): One to 2 months after 2 therapy sessions, during the blinded period, significantly improvement in sleep quality relative to baseline occurred in the active-MDMA arm (mean PSQI change [SD]: –3.53 [5.03]) relative to the control-MDMA arm (mean PSQI change [SD]: 0.56 [3.05]); P = 0.003 for between group difference; effect size (*Hedges g*) = 0.88). Compared to baseline, all participant's sleep quality significantly improved at treatment-end, and at 12 months of follow-up (these measurements did not have a control group as all participants had received active-MDMA). Improvements in PTSD severity scores were also reported.

Limitations (per authors): Small sample size; generalizability, given primarily white participants; subjective, self-reported outcome measurements

9. **Gorman I, Belser AB, Jerome L, et al. Posttraumatic Growth After MDMA-Assisted Psychotherapy for Posttraumatic Stress Disorder. *J Trauma Stress.* 2020;33(2):161-170.**

NCT not reported; includes data from studies MP-4 (not published), MP-8 (Mithoefer et al. 2018), and MP-12 (Ot'alora et al. 2018)

P: Adults with moderate-severe PTSD based on CAPS-4 total scores of ≥ 50 (MP-8 or MP-12) or ≥ 60 (MP-4) (Total n = 45 in the MDMA arm, and n = 15 in the placebo/low-dose MDMA arm)

I: MDMA 75-125 mg during the treatment therapy session x 2 plus co-team (male + female) 'manualized' therapy (three, 90-minute 'preparatory' sessions, two 8-hour treatment sessions ~1 month apart, which are each followed by three, 90-minute 'integration' sessions)

C: Placebo or low-dose 40 mg MDMA

O: Change in post-traumatic growth scores (measured by the 21-item PTG index, PTGI; total score ranges from 0 to 105) from baseline

T: Primary outcome was assessed 1 month after the 2nd MDMA/comparator treatment session. Additional follow-up was assessed after the cross-over period (participants crossover to MDMA 100-125 mg), and 12 months after the 3rd MDMA session (at that time all participants had been exposed to MDMA 100-125 mg three times plus therapy)

S: Pooled aggregate analysis of 3, phase 2 randomized triple-blind crossover trials (3 of 6 possible trials were selected since they measured posttraumatic growth)

Primary conclusion(s): At the end of the blinded period (after two, 75-125 mg MDMA doses plus therapy), MDMA-treated patients exhibited greater post-traumatic growth compared to patients receiving low-dose MDMA/placebo (Hedges *g* [a measure of standardized difference]: 1.14, 95%CI 0.49 to 1.78; P<0.001). At the longest follow-up (12 months), a time point for which there is not a control group, 67.2% of patients no longer met criteria for having PTSD.

Limitations (per authors): Pooled data from 3 different trials with slight differences in study design; possible unmasking of participants and/or therapists; scores on the PTGI are self-reported and not validated with observed behaviors; participants primarily identified as white.

10. **Jerome L, Feduccia AA, Wang JB, et al. Long-term follow-up outcomes of MDMA-assisted psychotherapy for treatment of PTSD: a longitudinal pooled analysis of six phase 2 trials. *Psychopharmacology.* 2020;237(8):2485-2497.**

    NCT00090064 (MP-1), **NCT00353938** (MP-2), **NCT01958593** (MP-4), **NCT01211405** (MP-8), **NCT01689740** (MP-9), **NCT017993610** (MP-12)

    P: Adults with moderate-severe PTSD (CAPS-4 score ≥ 50 or ≥ 60 in 1 trial)
    (Total *n* enrolled = 107; n = 91 completed long-term follow-up]

    I/C: *Varied by trial.* All participants were eventually exposed to 2-3 MDMA-assisted therapy sessions. There was not an untreated control for the longitudinal analysis.

    Initial higher-dose MDMA: *During blinded trial period*: MDMA [(75 mg, 100 mg, or 125 mg given as an initial dose + optional supplemental dose 1.5 to 2 hours later) two times, during treatment sessions] plus therapy by a male or female therapist co-team (three, 90-min 'preparatory' sessions pre-treatment plus two, 8-hour treatment sessions, separated by ~4 weeks plus three, 90-min 'integration' sessions); *during the unmasked crossover follow-up period*: MDMA active dose plus co-team led therapy (1 treatment session plus 3 'integration' sessions); two studies had only 2 MDMA therapy sessions (MP-1 and MP-9)

    Initial placebo or low-dose MDMA: *During blinded trial period:* inert placebo or low-dose (25-40 mg) MDMA; *during the crossover period:* MDMA 100-125 mg, 2-3 psychotherapy sessions (as per the intervention arm); in 2 studies (MP-2 and MP-9) participants completed 3 blinded sessions.

    O: Mean change from baseline in CAPS-4 total severity score

    T: Assessed at trial completion (after 2-3 MDMA sessions during the blinded or open-label period); long-term follow-up about 12 months after last MDMA therapy session (or 3.8 years in 1 trial)

    S: Within-group pooled analysis of 6 phase 2 RCTs that each included a parallel group double-blind period followed by a crossover and long-term follow-up periods; included sites in US, Canada, Switzerland, depending on the trial

    Primary conclusion(s): Significantly improved in PTSD symptoms (CAPS-4 total severity score) between baseline and completion of the 2-3 MDMA therapy sessions (LS mean [SE]: –44.8 [2.82]; P<0.0001), and between MDMA therapy completion a long-term follow-up (LS mean [SE]: –5.2.8 [2.29]; P<0.05); the estimated effect size (Cohen's *d*) was 1.58 and 0.23 for the aforementioned follow-up periods, respectively. Most participants described benefiting from treatment (56% did not meet PTSD diagnostic criteria at study completion), and "…a minority reported harms from study participation."[73]

    Limitations (per authors): Lack of untreated control for the analysis (*investigators examined within participant changes from baseline and considered the MDMA-exposed data for intervention and control patients*); for the long-term follow-up, some participants continued other interventions including therapy after the study period so any benefits could also be attributable to other treatments; population and intervention heterogeneity, though the statistical model adjusted for some potential covariates.

11. **Mithoefer MC, Feduccia AA, Jerome L, et al. MDMA-assisted psychotherapy for treatment of PTSD: study design and rationale for phase 3 trials based on pooled analysis of six phase 2 randomized controlled trials. *Psychopharmacology.* 2019;236(9):2735-2745.**

    NCT00090064, NCT00353938, NCT0195893, NCT01211405, NCT01689740, NCT01793610

    This study informed design of the phase 3 trials, influencing selection of 3 MDMA-assisted therapy sessions instead of 2.

    P: Adults with moderate-severe PTSD (CAPS-4 score ≥ 50 or ≥ 60 in 1 trial)
    (Total *n* enrolled = 105, with 8 (7.6%) of participants not completing the study)

I: *Varied by trial. During blinded period*: MDMA [(75 mg, 100 mg, or 125 mg given as an initial dose plus optional supplemental dose 1.5 to 2 hours later) two times, during treatment sessions] plus therapy by a male or female therapist co-team (three 90-minute 'preparatory' sessions pre-treatment plus two, 8-hour treatment sessions, separated by ~4 weeks plus three 90-minute 'integration' sessions); *during the unmasked crossover period*: MDMA active dose plus co-team led therapy (1 treatment session plus 3 'integration' sessions); two studies completed only 2 MDMA therapy sessions (MP-1 and MP-9)

C: *Varied by trial. During blinded period*: inert placebo or low-dose (25-40 mg) MDMA; *during the unmasked crossover period:* MDMA 100-125 mg, 2-3 psychotherapy sessions (as per the intervention arm); in 2 studies (MP-2 and MP-9), participants completed 3 blinded sessions

O: Mean change from baseline in CAPS-4 total severity score

T: Assessed at trial completion, 1-2 months after 2-3 MDMA-assisted treatment sessions

S: Pooled analysis of 6 phase 2 RCTs with similar study designs that included a parallel group double-blind period followed by a crossover and long-term follow-up periods; included sites in US, Canada, Switzerland, depending on the trial

Primary conclusion(s): Significantly improved in PTSD symptoms (CAPS-4 total severity score) between baseline and completion of 2 MDMA therapy sessions for the experimental group versus control group (mean between group difference [SE]: –22.0 [5.17]; P<0.001); the estimated effect size (Cohen's *d*) was 0.8. Investigators also describe improvements in the proportion of MDMA-treated participants versus control participants with symptoms meeting PTSD diagnostic criteria (statistical significance not reported), and in depression symptoms (not statistically significant). There is limited data limiting the ability to draw conclusions, but investigators report that there appears to be a greater proportion of treatment responders after 3 MDMA-assisted therapy sessions compared to 2 MDMA-assisted therapy sessions. Regarding safety, although considered well-tolerated overall, some AE were reported more frequently in the MDMA-treated versus control participants (eg, anxiety, dizziness, jaw clenching/pain, nausea, no appetite, depressed mood, irritability, and panic attack). Most AE were reported during the MDMA treatment sessions or within the week following the session.

Limitations (per authors): The majority of participants and therapists identify as white; population and intervention heterogeneity across the RCTs; risk of unblinding; during the third MDMA session, participants may have received MDMA while blinded or as open-label

3.2.3.1.6 Citations addressing the original pilot trial: Mithoefer et al. 2011 (NCT00090064)

12. **Mithoefer MC, Wagner MT, Mithoefer AT, Jerome L, Doblin R. The safety and efficacy of {+/-}3,4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: the first randomized controlled pilot study. *Journal of psychopharmacology*. 2011;25(4):439-452.**

P: Adults ages 21-70 years meeting DSM-IV-R criteria for crime or war-related, chronic moderate-severe PTSD (defined as a CAPS score ≥ 50), refractory to both 6+ months of psychotherapy and 3+ months of pharmacotherapy, following at least 3 months of psychotherapy after tapering and discontinuing all psychotropic medications except as-needed sedative-hypnotics or anxiolytics
(Total *n* randomized = 23)

I: MDMA 125 mg administered in two 8-10-hour experimental non-directive psychotherapy sessions 4 weeks apart (participants were also offered a supplemental MDMA 62.5 mg dose 2-2.25

hours after the initial dose). Each experimental session followed two 90-minute introductory sessions with therapists and was followed by an overnight stay. Each all-day session was followed by two 90-minute psychotherapy sessions the next morning and then weekly thereafter.

C: Inert placebo (lactose) administration with psychotherapy sessions that matched the active arm

O: Change in mean CAPS (versions not stated) score from baseline. Difference in percentages with clinical response from baseline.

T: Primary outcome measured at day 4 after each experimental session and 2 months after completion of the 2nd session

S: Randomized (60% MDMA: 40% placebo with replacement of any dropouts), double-blind, single-site (US), placebo-controlled trial

Primary conclusion(s): Significantly greater decrease in mean PTSD scale scores for MDMA versus placebo at all 3 time points. Rate of "clinical response" (defined as a >30% reduction in CAPS total score from baseline) was 10/12 (83%) with MDMA versus 2/8 (25%) with placebo. No serious drug-related adverse events, adverse neurocognitive effects, or blood pressure increases.

Limitations (per authors): Small sample size; homogenous sample of White female patients; baseline differences in prior psychotherapy that favored the treatment group; transparency of blinding for subjects

13. **Mithoefer MC, Wagner MT, Mithoefer AT, et al. Durability of improvement in post-traumatic stress disorder symptoms and absence of harmful effects or drug dependency after 3,4-methylenedioxymethamphetamine-assisted psychotherapy: a prospective long-term follow-up study. *Journal of psychopharmacology.* 2013;27(1):28-39.**

P: Adults with crime or war-related, treatment-refractory chronic, moderate to severe (ie, with baseline CAPS score of ≥ 50) PTSD, refer to Mithoefer et al. 2011.
(Total *n* randomized = 23; total n included in this descriptive extension study = 19)

I/C: There was not a comparator in this long-term, single-arm extension study of participants that received MDMA-assisted therapy during the blinded period followed by 1 additional MDMA-assisted therapy session in the unmasked period (initial MDMA arm), and participants that received 2-3 MDMA-assisted therapy during the open-label crossover period (initial placebo arm). In both arms, each experimental (placebo or MDMA) session followed two 90-minute introductory sessions with therapists and was followed by an overnight stay. Each all-day session was followed by two 90-minute psychotherapy sessions the next morning and then weekly thereafter.
Initial MDMA arm: MDMA 125 mg with an optional 62.5 mg dose 2-2.5 hours later (amendment allowed for approximately half of participants) administered in two 8-10-hour experimental psychotherapy sessions 4 weeks apart followed by a third open-label 8-10-hour experimental psychotherapy session 2 months following the second; or
Initial placebo arm: Inert placebo administered in two 8-10-hour experimental psychotherapy sessions 4 weeks apart, followed by open-label MDMA 125 mg with an optional 62.5 mg dose 2-2.5 hours later (amendment allowed for approximately half of participants) administered in two 8-10-hour experimental psychotherapy sessions 4 weeks

apart. Approximately half of participants also received a third 8-10-hour experimental MDMA-assisted therapy session.

O: Change from end-of-treatment in Clinician-Administered PTSD Scale (CAPS) since completion of the final MDMA session

T: Time to primary outcome varied from 17.3 to 74.3 months after completion of the final MDMA-assisted therapy session

S: Descriptive long-term follow-up of treated participants from a randomized, double-blind, single-site (US), placebo-controlled trial that was followed by an unmasked, crossover period

Primary conclusion(s): Mean CAPS scores were not statistically significantly different from end-of-treatment to long-term follow-up. Two participants relapsed during follow-up.

Limitations (per authors): Only 16 of 19 subjects completed long-term follow-up assessments; there was no meaningful control group; 8 of 19 subjects were still in psychotherapy and 12 of 19 were taking psychiatric medicines; small sample size.

14. **Corey VR, Pisano VD, Halpern JH. Effects of 3,4-Methylenedioxymethamphetamine on Patient Utterances in a Psychotherapeutic Setting. *J Nerv Ment Dis.* 2016;204(7):519-523.**
NCT not listed, but authors reported using data from the same trial as Mithoefer et al. 2011

P: Adults with refractory moderate-severe PTSD (baseline CAPS score ≥ 40) resulting from crime or war, refer to Mithoefer et al. 2011 (total n randomized = 23; participants with usable data for this analysis = 20)

I/C: See Mithoefer et al. 2011

O: Frequencies of patient utterances from therapeutic sessions that were empathic (regarding others' emotions), entastic (requesting or appreciating physical touch), or ensuic (describing a change in their sense of themselves) by blinded scorers

T: Primary outcome measures were taken during the first experimental therapeutic sessions (visit 5); CAPS scores were measured 4 days after this session.

S: Randomized, double-blind, single-site (US), placebo-controlled trial

Primary conclusion(s): Compared to placebo, MDMA-treated patients produced higher numbers of scored utterances versus placebo ($P<0.01$), including ensuic, empathic, and entactic utterances. A higher number of scored utterances correlated with lower posttreatment CAPS scores (Pearson's $r = –0.506$, $P=0.023$).

Limitations (per authors): None mentioned

15. **Wagner MT, Mithoefer MC, Mithoefer AT, et al. Therapeutic effect of increased openness: Investigating mechanism of action in MDMA-assisted psychotherapy. *J Psychopharmacol.* 2017;31(8):967-974.**
This study aimed to investigate the relationship between personality changes (neuroticism and openness) and improvement in PTSD symptoms as a secondary analysis of data from Mithoefer et al. 2011 and Mithoefer et al. 2013. ***Reporting of the methods and results is unclear, so the following is our best interpretation.***

P: Patients who participated in the MDMA-assisted study by Mithoefer et al. 2011 (ie, CAPS score ≥ 50 with refractory PTSD resulting from crime or war)
(Total n randomized = 23; participants with usable data for this analysis = 20; n = 16 providing long-term follow-up data)

I/C: Refer to Mithoefer et al. 2011. After the 2-month double-blinded period, placebo patients were allowed to receive 2 experimental MDMA-assisted therapy sessions (2 experimental MDMA sessions and 11 non-drug sessions) as per the MDMA arm during the original blinded period. A smaller proportion of patients were also assigned to a 3rd open-label MDMA-assisted therapy session (1 experimental session plus 3 non-drug sessions; n = 5 initially MDMA-assigned patients, and n = 4 initially placebo-assigned patients).

O: Change in Openness and Neuroticism Scales of the Revised NEO Personality Inventory (NEO PI-R) from baseline to 2 months and long-term follow-up. Global CAPS scores at 2 months and long-term follow-up while adjusting for change in Openness or Neuroticism from baseline to 2 months using repeated measure ANOVA.

T: Primary outcome measured at 2 months and long-term follow-up (mean 45.4 months)

S: Subgroup analysis using data from a randomized, double-blind, single-site (US), placebo-controlled trial, and a long-term, single-arm open-label follow-up of the trial

Primary conclusion(s): At 2-month follow-up, differences in CAPS scores were no longer significant for MDMA versus placebo when controlling for change in Openness scores (P=0.246); by contrast, CAPS score decreases remained significantly better for MDMA versus placebo when controlling for Neuroticism scores (P=0.02). At long-term follow-up of participants that all received MDMA-assisted therapy (ie, including MDMA and initially placebo arms), there were significant changes in Neuroticism and Openness compared to baseline (P<0.05).

Limitations (per authors): Patients and therapists were able to correctly guess treatment assignments; main outcome measures are based on subjective report; sample size was small.

3.2.3.2 MDMA for Social Anxiety Disorder in Autistic Adults (NCT02008396)

16. Danforth AL, Grob CS, Struble C, et al. Reduction in social anxiety after MDMA-assisted psychotherapy with autistic adults: a randomized, double-blind, placebo-controlled pilot study. *Psychopharmacology.* 2018;235(11):3137-3148.

P: *Autistic* adults (age ≥ 21 years) with social anxiety disorder (Liebowitz Social Anxiety Scale [LSAS] score ≥ 60)
(Total *n* randomized = 12)

I: MDMA-assisted therapy, including MDMA at escalating doses per experimental session: 4 participants received MDMA 75 mg followed by 100 mg, and the other 4 received MDMA 100 mg followed by 125 mg. Therapy included 3 'preparatory' sessions (60-90 minutes each) plus 2 experimental MDMA sessions (about 8 hours each) separated by 1 month, which were followed by 3 'integrative' therapy sessions (60-90 minutes each) and were separated by 1 week. Preparatory and integrative therapy sessions followed a "standardized mindfulness-based therapy"[74] approach.

C: Matched inert placebo plus therapy as per the MDMA arm

O: Mean difference in LSAS score from baseline to follow-up; standardized placebo-corrected effect size calculated using Cohen's *d*

T: Primary outcome was 1 month after the 2nd MDMA session. Differences from baseline to 6 months were also calculated.

S: Phase 2, dose-finding, single-site (US), randomized (2 MDMA:1 placebo), placebo-controlled, double-blind trial. Blinding ended at 6 months; at this time, placebo patients were allowed to receive 2 MDMA-assisted therapy sessions.

Primary conclusion(s): Greater improvement in social anxiety symptoms from baseline to 1 month and 6 months after the last MDMA session for MDMA-treated participants compared to placebo-treated participants (mean change from baseline to 1 month [SD]: MDMA, –44.4 [14.8]; placebo, –19.3 [18.8]; P=0.037 for between-group difference; mean change from baseline to 6-months [SD]: MDMA, –47.7 [14.7]; placebo, –23.2 [18.0]; P=0.036 for between-group difference). The treatment effect size (Cohen's *d* [95%CI]) at 1-month was 1.4 [–0.074 to 2.874], and 1.1 [–0.307 to 2.527] at 6 months.

Limitation(s): Small sample size; and participants were heterogeneous at baseline with regard to social anxiety severity and other psychiatric conditions.

3.2.3.3 MDMA for Anxiety Associated with Life-threatening Illness (NCT02427568)

17. **Wolfson PE, Andries J, Feduccia AA, et al. MDMA-assisted psychotherapy for treatment of anxiety and other psychological distress related to life-threatening illnesses: a randomized pilot study. *Scientific reports.* 2020;10(1):20442.**

P: Adults (mean age of 55 years) with moderate-severe anxiety (baseline State Trait Anxiety Inventory [STAI]-Trait subscale score of ≥ 45) associated with life-threatening non-brain cancer, or non-dementing neurological illness that could safely taper off psychiatric medications. Confirmation of illness-associated anxiety was confirmed by structured interview to confirm DSM-IV criteria. Many participants had a history of anxiety (83.3%), MDD (77.8%), PTSD (72.2%) and insomnia (61.1%). (Total *n* randomized = 18; 17 participants completed long-term follow-up)

I: *Blinded period:* MDMA 125 mg administered during two 8-hour experimental non-directive psychotherapy sessions separated by 2-4 weeks plus 9 non-drug 60-90 minute psychotherapy sessions. An optional second MDMA 62.5 mg dose 1.5 to 2.5 hours the initial dose was available. MDMA-assisted therapy sessions were preceded by 3 'preparatory' therapy sessions, and 'integrative' therapy sessions occurred the day after the experimental sessions and 2 additional times over the following month. Therapists also contacted participants for daily phone calls during the 7 days after an experimental session. *Crossover period:* participants received 1 additional MDMA-assisted therapy session and 3 integrative therapy sessions.

C: *Blinded period:* Matched inert placebo administered during two 8-hour experimental non-directive psychotherapy sessions with therapy sessions as per the MDMA arm. *Crossover period:* participants received a preparatory session followed by 2 MDMA-assisted therapy sessions with 3 integrative therapy sessions, and 1 additional MDMA-assisted therapy session/3 integrative session about 1 month later.

O: Mean change in STAI-trait subscale score. Change in STAI-state subscale score was a secondary outcome.

T: The primary outcome was change in STAI score from baseline to 1 month after the second blinded drug-assisted therapy session. STAI scores were also measured for long-term follow-up at 6 months and 12 months after the last MDMA-assisted therapy session for all participants (ie, initial MDMA arm and initial placebo arm).

S: Phase 2, randomized (3 MDMA: 1 placebo), single-site (US outpatient clinic), double-blinded, placebo-controlled clinical trial. After the double-blinded period, there was an unmasked crossover period followed by an uncontrolled, single-arm, long-term follow-up period.

Primary Conclusion(s): There was a non-statistically significant reduction in anxiety symptoms (STAI-Trait score) from baseline to 1 month after 2 drug-assisted therapy session for MDMA compared to placebo (mean change from baseline [SD]: MDMA, –23.5 [13.2] versus placebo, –8.8 [17.9]; P =

0.0558 for the between-group difference; between-group effect size [Hedges *g*] = 1.03, 95%CI –5.25 to 7.31). A similar non-statistically reduction for the secondary outcome of STAT-state scores for MDMA compared to placebo occurred (mean change from baseline to 1 month after last treatment [SD]: MDMA, –22.1 [17.9] versus placebo, –6.0 [15.8]; P = 0.10 for the between-group difference). At 6-month and 12-month follow-up, the mean STAI-Trait and mean STAI-state scores among all participants were statistically significantly lower than baseline (P<0.0001 for both). Investigators considered MDMA to be well-tolerated by participants, with most treatment-emergent adverse events occurring more frequently with MDMA compared to placebo resolving within 1 week.

Limitations (per authors): Small sample size, lacking power to detect statistical significance; potential outlier in placebo group that responded unusually well to placebo psychotherapy; lack of diversity due to participants being primarily White females; long-term follow-up results lacked a control group and blinding that limits usefulness and interpretation of those results.

3.2.3.4 Other MDMA Citations

18. **Curran HV, Wall M, Demetriou L, Carhart-Harris R, Fergusson B, Nutt D. S.23.02 - Effects of ecstasy on autobiographical memories: implications for MDMA assisted psychotherapy.** ***European Neuropsychopharmacology.*** **2016;26:S145.**

NCT not reported

Limited information is available since it is published as an abstract only. We could not verify that the study meets all eligibility criteria (eg, randomization, patient population with a mental health condition).

P: Not reported

I: MDMA-HCl 100 mg

C: Placebo

O: Recall and encoding of memories; measured by functional MRI (fMRI) and self-referent encoding (SRE) of descriptors in reference to oneself vs others (considered "neutral")

T: Not reported

S: Double-blinded trial with repeated measures using functional MRI imaging

Primary conclusion(s): Participants administered MDMA exhibited a significant reduction in medial prefrontal cortex/left insula activation during self-referential activities compared to people receiving placebo. There was enhanced hippocampal activity during favorable memories versus enhanced executive activity during negative memories among MDMA recipients; they rated favorable memories as more positive and negative memories as less negative compared to placebo recipients.

Limitations (per authors): Not reported

3.2.4 Psilocybin Studies

3.2.4.1 Psilocybin for Depression

3.2.4.1.1 Citations addressing the original phase 2b trial: Goodwin et al. 2022 (NCT03775200)

19. **Goodwin GM, Stansfield SC, Hellersten DJ, et al. The safety and efficacy of COMP360 psilocybin therapy in treatment-resistant depression: results from a phase IIb randomized controlled trial. Poster presented at: 2022 American Psychiatric Association Meeting; May 2022; New Orleans, LA.**

This is from a poster presented at a conference; fewer details are available, and it has not been peer-reviewed for publication in a journal.

P: Adults with moderate-severe (Hamilton Depression Rating Scale [HAM-D] score ≥ 18) treatment-resistant major depression. A 2-week antidepressant washout period preceded the trial.

(Total *n* randomized = 233)

I: Compass proprietary psilocybin (COMP360) 25 mg or 10 mg x 1 dose with one, 6-8 hour psychotherapy support session by a trained therapist during psilocybin administration

C: Low-dose (1 mg) Compass proprietary psilocybin (COMP360) x 1 dose with one, 6-8 hour psychotherapy support session by a trained therapist during psilocybin administration

O: The primary outcome was the least squares mean change from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) total score; a key secondary outcome was the persistence of a sustained response (maintenance of ≥ 50% change in MADRS total score from baseline)

T: The primary outcome was measured 3 weeks after the psilocybin dose, and the key secondary outcome was assessed at week 12. The MADRS total score was assessed at baseline, day 2, week 1, week 3, week, 6, week 9, and week 12.

S: International, multisite, randomized (1:1:1), double-blind, active-controlled, phase IIb trial

Primary conclusion(s): Psilocybin 25 mg, but not 10 mg, was superior to psilocybin 1 mg for improvement in depression symptoms (change in MADRS total score from baseline) 3 weeks after 1 dose (25 mg versus 1 mg, least squares mean difference in change in score [95%CI]: –6.6 [– 10.2 to –2.9]; P<0.001). Numerically greater improvement in depression symptoms for 25 mg versus 1 mg were apparent on day 2 and 1 week after psilocybin treatment (no statistical analysis reported). The proportion of participants with a sustained response (assessed for week 12 versus week 3) were 16/79 (20.3%), 4/75 (5.3%), and 8/79 (10.1%), for the 25 mg, 10 mg, and 1 mg arms, respectively (no statistical analysis reported). Dose-related treatment-emergent AE included headache, nausea, and dizziness. From day 2 to week 3, and after week 3 to week 12, there was a numerically (a statistical analysis was not reported) higher incidence of treatment-emergent serious adverse events (TESAE) in the psilocybin 25 mg and 10 mg arms, relative to the psilocybin 1 mg arm. The incidence of any TESAE from day 2 to week 3 was as follows: 5.1%, 5.3%, and 0% for 25 mg, 10 mg, and 1 mg, respectively. Events during this period included suicidal ideation, intentional self-injury, and hospitalization. The incidence of any TESAE from after week 3 to week 12 was as follows: 5.1%, 4.0%, and 1.3% for 25 mg, 10 mg, and 1 mg, respectively. Events during this period included suicidal behavior (reported for the 25 mg arm, but not the other arms), intentional self-injury (reported in the 10 mg and 1 mg arms), adjustment disorder, depression, drug withdrawal syndrome, and suicidal ideation. The investigators report that there was not any clinically significant changes in laboratory results or vital signs; a few patients in the psilocybin 25 mg arm experienced acute, transient changes in the cardiac QTcF interval.

Limitations (per authors): Not reported

20. Goodwin GM, Aaronson S, Dunlop BW et al. A multicenter, international, phase IIb randomized controlled trial of COMP360 psilocybin therapy in treatment-resistant depression: Changes in affect, anxiety, and further exploratory endpoints. Poster presented at: 2022 American Society of Clinical Psychopharmacology meeting; June 2022; Scottsdale, AZ.

This is from a poster presented at a conference; fewer details are available, and it has not been peer-reviewed for publication in a journal.

P: Adults with moderate-severe (HAM-D score ≥ 18) treatment-resistant major depression. A 2-week antidepressant washout period proceeded the trial. (Total n randomized = 233)

I: Compass proprietary psilocybin (COMP360) 25 mg or 10 mg x 1 dose plus one, 6-8 hour psychotherapy support session by a trained therapist during psilocybin administration

C: Low-dose (1 mg) Compass proprietary psilocybin (COMP360) x 1 dose plus one, 6-8 hour psychotherapy support session by a trained therapist during psilocybin administration

O: Multiple exploratory outcomes; change from baseline on the following scales: positive and negative affect schedule (PANAS), generalized anxiety disorder scale - 7 items (GAD-7), work and social adjustment scale (WSAS), Sheehan disability scale (SDS), EQ-5D-3L and EQ visual analog scale (VAS), and digit symbol substitution test (DSST)

T: Outcomes assessed 3 weeks following the psilocybin dosing session

S: *Exploratory,* secondary analysis of an international, multisite, randomized (1:1:1), double-blind, active-controlled, phase IIb trial

Primary conclusion(s): Relative to baseline, at 3 weeks, the high-dose psilocybin arm (25 mg) exhibited significantly greater improvements in multiple exploratory outcomes compared to the low-dose comparator (1 mg). These outcomes (expressed as least squares mean difference in change from baseline [LSMD] for 25 mg versus 1 mg) included PANAS positive affect score (6.2, 95%CI 3.5 to 8.8), PANAS negative affect score (–3.2, 95%CI –5.6 to –0.8), GAD-7 score (–1.8, 95%CI –3.4 to –0.2), WSAS score (–5.1, 95%CI –8.4 to –1.8) and SDS score (–6.5, 95%CI –9.5 to –3.5). Statistical tests for differences for psilocybin 10 mg versus 1 mg were not reported, but the numerical changes from baseline for 10 mg were smaller than for 25 mg. No significant differences between treatment arms were observed for the quality of life (EQ-5D-3L) or cognition measure (DSST).

Limitations (per authors): Not reported

21. **Goodwin GM, Aaronson S, Dunlop BW et al. A multicenter, international, phase IIb randomized clinical trial of COMP360 psilocybin therapy in treatment-resistant depression: Response and remission rates. Poster presented at: 2022 American Society of Clinical Psychopharmacology; June 2022; Scottsdale, AZ**.

This is from a poster presented at a conference; fewer details are available, and it has not been peer-reviewed for publication in a journal.

P: Adults with moderate-severe (HAM-D score ≥ 18) treatment-resistant major depression. A 2-week antidepressant washout period preceded the trial. (Total n randomized = 233)

I: Compass proprietary psilocybin (COMP360) 25 mg or 10 mg x 1 dose plus one, 6-8 hour psychotherapy support session by a trained therapist during psilocybin administration

C: Low-dose (1 mg) Compass proprietary psilocybin (COMP360) x 1 dose plus one, 6-8 hour psychotherapy support session by a trained therapist during psilocybin administration

O: Treatment response (≥ 50% change), remission (MADRS total score ≤ 10), and sustained response (treatment response sustained to week 12) rates based on change from baseline in the MADRS total score (key secondary endpoints); and change from baseline in QIDS-SR-16 (Quick Inventory of Depression Symptomatology-Self-Rated 16-item scale) total score (exploratory endpoint)

T: Response, remission, and QIDS-SR-16 scores were assessed at 3 weeks post-treatment. Sustained response was assessed at 12 weeks.

S: Analysis of 3 key secondary endpoints from an international, multisite, randomized (1:1:1), double-blind, active-controlled, phase IIb trial

Primary conclusion(s): Three weeks after treatment, the proportion of treatment responders relative to baseline was as follows: 25 mg (36.7%, 29/79) versus 1 mg (17.7%, 14/79). And the proportion of treatment remitters relative to baseline was as follows: 25 mg (29.1%, 23/79) vs 1 mg (7.6%, 6/79). Sustained responders, the percent meeting response criteria on the MADRS scale at 3 weeks, 12 weeks, and 6 or 9 weeks, were as follows: 25 mg (24.1%, 19/79) versus 1 mg (10.1%, 8/79). The percent of responders, remitters, and sustained responders was similar between psilocybin 10 mg and 1 mg arms. Investigators report the results for the percent responders and remitters descriptively, without a statistical analysis. At week 3 relative to baseline, change in

depression symptoms in the past week (QIDS-SR-16) was significantly greater in the 25 mg arm than the 1 mg arm (least squares mean difference: –2.8 [95%CI –4.6 to –0.9]).

Limitations (per authors): Not reported

22. **Goodwin GM, Marwood L, Mistry S et al. COMP360 psilocybin therapy in treatment-resistant depression: Results of a large randomized controlled phase IIb monotherapy study and an exploratory adjunctive therapy study. Poster presented at: 2022 American Society of Clinical Psychopharmacology; June 2022; Scottsdale, AZ.**

This is from a poster presented at a conference; fewer details are available, and it has not been peer-reviewed for publication in a journal. This poster included results from 2 clinical trials: one is the phase 2b randomized, blinded, controlled trial (NCT03775200) and the other was a phase 2, open-label single arm trial of a small group of patients with treatment-resistant depression that received psilocybin 25 mg in addition to a serotonergic antidepressant (NCT04739865) that does not meet our criteria for the annotated bibliography.

P/I/C/O/T/S: See Goodwin GM et al.

Additional safety conclusion(s): The incidence of treatment-emergent adverse effects (TEAEs) per study arm during the entire double-blinded, controlled trial period (anytime through 12 weeks) was as follows: 25 mg (83.5%), 10 mg (74.7%), and 1 mg (72.2%). On day 1 (psilocybin dosing day), the most frequent TEAEs occurring numerically more with psilocybin 25 mg than psilocybin 1 mg were headache and nausea. Although a serious suicidal ideation/behavior occurred (including 3 cases >4 weeks after psilocybin 25 mg, among patients lacking improvement in depression symptoms), investigators reported that mean change from baseline for the MADRS suicidal ideation item did not worsen for any treatment arm, and the change from baseline to worst reported Columbia-Suicide Severity Rating Scale Score was not worse in the 25 mg or 10 mg arm relative to 1 mg arm (details for these measurements were not reported).

Limitations (per authors): Not reported

3.2.4.1.2 Citations addressing the original phase 2 clinical trial: Carhart-Harris et al. 2021 (NCT03429075)

23. **Carhart-Harris R, Giribaldi B, Watts R, et al. Trial of Psilocybin versus Escitalopram for Depression. *The New England journal of medicine.* 2021;384(15):1402-1411.**

P: Adults (18 to 80 years old) with moderate to severe major depression (HAM-D 17 score ≥ 17 at baseline) without prior use of escitalopram. Other psychiatric treatments were discontinued ≥ 2 weeks, and psychotherapy was discontinued ≥ 3 weeks prior to starting the study drugs.
(Total *n* randomized = 59)

I: Psilocybin 25 mg x 2 doses separated by 3 weeks given with daily matched placebo; patients also received psychological support consisting of at least 6 visits over 6 weeks with a two-person therapist team. These visits included a preparatory visit 1 day before the drug-assisted session, a well-being focused support session during drug administration session 1, psychological debriefing 1 day after the drug session; and 3 weeks later, a similar drug administration session, followed by an integrative therapy session ("…involving open, attentive listening") the next day, and a final psychological debriefing session 3 weeks later.

C: Escitalopram 10 mg daily titrated to 20 mg after 3 weeks given with psilocybin 1 mg x 2 doses separated by 3 weeks, given when the psilocybin 25 mg arm received their psilocybin dose; patients also received psychological support as per the psilocybin 25 mg arm.

O: Change in Quick Inventory of Depressive Symptomatology-Self-Report 16 items (QIDS-SR-16) score from baseline

T: The primary outcome was assessed at 6 weeks

S: Phase 2, parallel-group, randomized (1:1), double-blind, active-controlled trial

Primary result(s): At 6 weeks, change in depression symptom scores were similar between psilocybin- and escitalopram-treated participants (between group difference in change in scores from baseline: 2.0 points; 95%CI –5.0 to 0.9; P = 0.17). Secondary outcomes, such as response (ie, severity score reduced by >50%), tended to favor psilocybin. The incidence of adverse events was also similar in both treatment arms.

Limitations (per authors): No adjustment for multiple comparisons; short duration of use of escitalopram relative to its time to onset of effect; no assessment of blinding adequacy; and generalizability concerns due to a high proportion of patients being self-recruited (perhaps high interest in psilocybin), limited diversity of ethnic and socioeconomic backgrounds, and the severity of depression at baseline (most patients classified as moderate).

24. **Daws RE, Timmermann C, Giribaldi B, et al. Increased global integration in the brain after psilocybin therapy for depression. *Nature medicine.* 2022;28(4):844-851.**

This study reported results from a single-arm psilocybin trial, and from a blinded RCT (ie, NCT03429075*). We focus on results contrasting the psilocybin and escitalopram arms from the blinded RCT. It is unclear, but it appears that this analysis was limited to within-group changes from baseline.*

P: Adults with unipolar moderate-severe MDD; in the open-label single-arm trial, participants had treatment-resistant depression
(Total *n* = 21 patients receiving escitalopram, and 22 receiving psilocybin because some participants were excluded due to excessive head motion that interfered with measurements; the open-label trial included 16 participants)

I/C: Refer to Carhart-Harris et al. 2021. Open-label trial participants also received 2 doses of psilocybin (first 10 mg, then 25 mg) separated by 1 week.

O: Functional connectivity with a Pearson correlation coefficient calculated for mean signal fluctuations, transformed to Z scores. Brain network modularity, functional cartography, and dynamic flexibility were also calculated from functional magnetic resonance imaging (fMRI) data.

T: fMRI at baseline and 3 weeks and 1 day after psilocybin dose 2 (about 6 weeks from baseline); fMRI measurements for the open-label cohort were 1 day after the second dose of psilocybin

S: Eyes-closed fMRI data was collected from 2 clinical trials: (1) an open-label single-arm trial; and (2) a phase 2, randomized, blinded, active-controlled trial

Primary conclusion(s): There were decreases in brain network modularity (ie, increased flexibility) 3 weeks after the last dose of psilocybin relative to baseline among psilocybin-treated participants in the blinded trial (mean difference [95%CI]: –0.39 [–0.75 to –0.02]; P = 0.039; *d* = 0.47). In contrast, a significant difference between baseline and 3 weeks after treatment was not observed among escitalopram-treated participants (mean difference [95%CI]: –0.01 [–0.35 to 0.33]; P = 0.95; *d* = 0.02). In the psilocybin arm, improvement in depression severity correlated with the reduced network modularity; this correlation was not observed for escitalopram-treated patients. Similar results for psilocybin-correlated changes were observed in both trials.

Limitations (per authors): It is possible that psilocybin-mediated effects occur via a mechanism other than those calculated in this study; possibility of confounding due to fMRI collection methods (eg, possibility of head motion, or sleeping in the MRI), although authors designed the protocol to minimize these effects; failure to replicate "finer-grained cartography analyses"[75]; difficulties collecting sufficiently powered fMRI data, although others felt they were powered to estimate correlations.

3.2.4.1.3 Citations addressing the original clinical trial: Davis et al. 2021 (NCT03181529)

25. **Davis AK, Barrett FS, May DG, et al. Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder: A Randomized Clinical Trial. *JAMA psychiatry.* 2021;78(5):481-489.**
    P: Adults 21-75 years old with untreated moderate to severe MDD (GRID-HAMD score ≥ 17). (Total *n* randomized = 27)
    I: Immediate treatment: 2 escalating oral psilocybin doses (20 mg/70 kg and 30 mg/70 kg) administered a mean of 1.6 weeks apart in two, 11-hour supportive psychotherapy sessions; interventions were administered after two 8-hour preparatory sessions; 'supportive psychotherapy' included the availability of 2 facilitators with varying education levels (eg, bachelor's, master's, doctorate, and medical degrees) and professional disciplines (eg, social work, psychology, and psychiatry) to respond to participants' physical and emotional needs during the 11-hour sessions.
    C: Delayed treatment: no intervention other than weekly brief in-person or phone calls for assessment of symptoms was administered to wait-listed patients (controls) until after 8-week trial period
    O: Standardized mean difference (SMD) of change from baseline in GRID-HAMD scores (calculated using Cohen's *d*)
    T: Primary outcome measured 1 and 4 weeks after completion of 2nd psilocybin treatment (corresponding to week 5 and week 8 from baseline)
    S: Randomized (1:1 urn randomization[§] balancing age, sex, depression severity, and treatment resistance), open label, single-site (US), controlled (wait listed patients) trial
    Primary conclusion(s): Significantly greater improvement in GRID-HAMD scores associated with psilocybin treatment (P<0.001 for between-group difference in means at week 5 and week 8). Mean (SD) GRID-HAMD scores in the treatment group were 22.9 (3.6) at baseline and 8.0 (7.1) and 8.5 (5.7) at 1 and 4 weeks after treatment, respectively, versus 22.5 (4.4), 23.8 (5.4), and 23.5 (6.0) in the delayed-treatment group (ie, untreated wait-list comparators). Limited mild and transient adverse effects were observed during treatment sessions including blood pressure elevation (1 participant) and headache (33%).
    Limitations (per authors): Antidepressants may have been prescribed by non-study clinicians; lack of blinding and 11% attrition[**]; short follow-up; small sample predominantly composed of White non-Hispanic participants; participants had low suicide risk and moderately severe depression; lack of placebo control; varying professional disciplines of facilitators, often lacking formal clinical training

26. **Gukasyan N, Davis AK, Barrett FS, et al. Efficacy and safety of psilocybin-assisted treatment for major depressive disorder: Prospective 12-month follow-up. *Journal of psychopharmacology.* 2022;36(2):151-158.**
    P: Adults 21-75 years old with untreated moderate to severe MDD (GRID-HAMD score ≥ 17) (Total *n* randomized = 27; 24 participants included at follow-up)
    I/C: Refer to Davis et al. 2021. At the time of long-term follow-up, all participants had received 2 oral psilocybin doses with 'supportive psychotherapy,' so there was not a long-term comparator arm.
    O: Standardized mean difference (SMD) of change from baseline GRID-HAMD scores (calculated using Cohen's *d*)
    T: Primary outcome was measured 3, 6, and 12 months after the 2nd psilocybin treatment
    S: Single-arm, open-label (with blinded outcome evaluator) follow-up of a randomized, controlled trial

[§] Urn randomization is a method of generating random assignment while balancing up to 20 baseline characteristics
[**] Limitation(s) added by writers of this report that were not reported by investigators in the publication.

Primary conclusion(s): Findings support the *potential* durability of improvement in GRID-HAMD scores from baseline to 3-, 6-, and 12-months (Cohen *d* = 2.0, 2.6, 2.4, respectively). No drug-related serious adverse events occurred.

Limitations (per authors): About one-third of participants endorsed use of confounding medications (antidepressants) during the period between study completion and follow-up; lack of untreated comparator during the follow-up period; effectiveness could also be due to "expectancy effects", and this placebo-effect could be long-lasting; generalizability to patients underrepresented in the study population (eg, ethnicity other than White non-Hispanic) including higher-risk patients based on suicidality; small sample size.

27. **Barrett F. In patients with major depressive disorder, psilocybin administration is associated with reduced amygdala response to negative affective stimuli and normalization of cortical glutamate one week after psilocybin, and improved cognitive flexibility one and four weeks after psilocybin.** ***Neuropsychopharmacology.*** **2019;44:76-77.**

NCT not reported, but based on the methods and authors, we believe these results to be from the same trial reported by Davis et al. 2021. *Published as an abstract only, limiting available information about the study. It is unclear whether investigators calculated within-group changes for all participants, or if the results contrast the immediate and delayed treatment groups prior to the delayed group receiving psilocybin.*

P: Adults (mean age=40.3 years) diagnosed with MDD (total *n*=21; immediate treatment (n=12), or delayed (n=9) psilocybin treatment).

I: Immediate treatment with psilocybin in two administration sessions of different dosing (session 1: 20 mg/70 kg; session 2: 30 mg/70 kg).

C: Delayed treatment with psilocybin in two administration sessions of different dosing (session 1: 20 mg/70 kg; session 2: 30 mg/70 kg).

O: The primary outcome is unclear. Authors report measuring cognitive flexibility using the Penn Conditional Exclusion Task (PCET) and verbal reasoning using the Penn Verbal Learning Test (n = 18 participants with measurements). In addition, for a subset of participants, proton magnetic resonance spectroscopy (MRS) of the anterior cingulate (n=10), right hippocampus (n=10), left hippocampus (n=7), and amygdala reactivity (n=12) was performed. Amygdala measurements occurred during a reactivity task to emotional facial expressions.

T: Measurements were collected at baseline (3 weeks before psilocybin session 1), and after psilocybin session 2 (1 week and 4 weeks later) for the PCET and verbal learning test. MRS was completed at baseline and 1 week after psilocybin session 2.

S: Randomized (via Urn randomization), waitlist-controlled trial. Outcomes were measured in a subset of trial participants that varied by the measurement.

Primary conclusion(s): Compared to baseline, measurements of glutamate were higher in the right hippocampus (*d* = 0.59; P not reported), and lower in the anterior cingulate cortex (*d* = 0.53; P not reported*)* at 1 week after the 2nd psilocybin administration. In the amygdala, the response to negative affective stimuli was lower 1 week after psilocybin dosing session 2 compared to baseline (*d* = 0.61; P=0.026). The changes in amygdala BOLD intensity signals in response to negative stimuli correlated with a reduction in depression severity (per GRID-HAMD) measured at 1 week after psilocybin dosing session 2 (r=0.417). Cognitive flexibility improved from baseline to 1 week (P=0.045) and 4 weeks (P = 0.016) after the 2nd psilocybin treatment. No changes in verbal reasoning were observed.

Limitations (per authors): Not reported.

3.2.4.2 Psilocybin for Psychological Distress, Depression, or Anxiety Associated with Life-threatening Cancer

3.2.4.2.1 Citations addressing the original clinical trial: Griffiths et al. 2016 (NCT00465595)

28. Griffiths RR, Johnson MW, Carducci MA, et al. Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. *Journal of psychopharmacology.* 2016;30(12):1181-1197.

P: People (mean age = 56.3 years) with life-threatening cancer and depression or anxiety diagnoses meeting DSM-IV criteria
(Total *n* randomized = 56)

I: High-dose psilocybin first: oral psilocybin (22 or 30 mg/70 kg) administered in the context of monitored, 'nondirective' and 'supportive' therapeutic sessions of unspecified duration. Interventions were administered after two to three 8-hour preparatory sessions; monitors had varying education levels and professional qualifications.

C: Active-placebo psilocybin first: oral low (placebo-like) dose of psilocybin (1-3 mg/70 kg), masked to resemble the intervention, administered in therapeutic sessions matching the intervention arm

O: Change, SMD of change (Cohen's d), and percentage with clinically-significant change (ie, ≥50% decrease) in GRID-HAMD scores (depression) and HAM-A (anxiety) versus baseline

T: Primary outcome measured 5 weeks after the psilocybin treatment session

S: Randomized (1:1), masked inactive controlled, double-blind (participants and monitors), crossover, single-site (US) trial. In this crossover trial, participants were randomized as to whether they received the intervention in the first session, or the 2nd session 5 weeks later.

Primary conclusion(s): Significant improvement from baseline in GRID-HAMD and HAM-A scores in both groups 5 weeks after the first sequence ($P<0.05$). SMDs of GRID-HAMD and HAM-A were significantly larger for high-dose versus control ($P<0.001$). Percentages with clinical response were 92% for high-dose treatment versus 32% for control ($P<0.01$). Mean GRID-HAMD scores (standard error of the mean [SEM]) for high-dose treatment were 22.9 (1.0) at baseline and 6.6 (1.0) at 5 weeks versus 22.3 (0.9) and 14.8 (4.5) for control. Mean HAM-A scores (SEM) for high-dose treatment were 25.7 (1.1) at baseline and 8.5 (1.2) 5 weeks after treatment versus 25.7 (0.9) and 16.6 (1.5) for control. Mild and transient adverse effects observed during treatment sessions including blood pressure elevations, nausea/vomiting, and psychological distress; no hypothesis testing was conducted on adverse effects.

Limitations (per authors): Session monitors varied in training and clinical backgrounds and 8.6% attrition at week 5 outcome assessment[††]; no statistical comparisons were made for adverse event risks; low-dose control may have been high enough to have some therapeutic activity; study not designed to assess efficacy beyond 5 weeks; study sample was small and homogenous.

3.2.4.2.2 Citations addressing the original clinical trial: Ross et al. 2016 (NCT00957359)

29. Ross S, Bossis A, Guss J, et al. Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. *Journal of psychopharmacology.* 2016;30(12):1165-1180.

[††] Limitation(s) added by writers of this report that were not reported by investigators in the publication.

P: Adults (mean age 56.3) with cancer (62% with stages III or IV) and an anxiety-related diagnosis of either adjustment disorder with or without depressed mood or generalized anxiety disorder (per Structured Clinical Interview for DSM Disorders [Diagnostic and Statistical Manual of Mental Disorders-IV]). Most (59%) of participants reported previous treatment with an antidepressant or anxiolytic agent, but no participants were on any psychotropic agents at the time of enrollment. (Total *n* randomized = 29).

I: Psilocybin-first: single dosing session of oral psilocybin (0.3 mg/kg) plus psychotherapy, followed by a single dose of oral niacin 250 mg 7 weeks later. Therapy consisted of 3 preparatory sessions (6 hours total) occurring 2-4 weeks before the psilocybin dose; 3 integrative session (6 hours total) occurring over 7 weeks following the psilocybin dose; and 3 additional integrative sessions (6 hours total) occurring within 6 weeks after the niacin dose. Psychotherapy sessions and post-medication integration sessions were conducted by a dyadic psychotherapy team.

C: Niacin first: single dosing session of oral niacin 250 mg plus psychotherapy followed by a single dose of oral psilocybin (0.3 mg/kg) 7 weeks later. Therapy was the same as the psilocybin-first arm.

O: Pre-crossover mean score on various anxiety or depression scales, including: (1) Hospital Anxiety and Depression Scale [HADS] total score; (2) patient-reported anxiety (HADS-A); (3) depression (HADS-D); (4) Beck Depression Inventory (BDI); and Spielberger State-Trait Anxiety Inventory (STAI), including (5) patient-reported levels of the anxiety state (STAI-S) and (6) trait (STAI-T).

T: The primary outcome variables were measured prior to the crossover at 1 day and 6 weeks after the first dosing session, and 1 day before the second dosing session. Additional measurements after crossover (ie, when all participants had received psilocybin) were collected 1 day, 6 weeks and 26 weeks after the second dosing session.

S: Randomized, double-blind, controlled, crossover, single-site (US) trial. Patients were randomized to the sequence of interventions to receive either psilocybin or niacin first. The second dosing session (administration of the alternative therapy from the first) occurred 7 weeks after the first session.

Primary conclusion(s): Prior to crossover, mean scores for each of the primary outcome measures of anxiety and/or depression were significantly lower at each time point (1 day to 7 weeks after the first dosing session) for the psilocybin-first arm compared to the niacin-first arm (P varied from $P<0.05$ to $P\leq0.001$, depending on the scale and time point). The between-group effect size (Cohen's *d*) for the primary outcome measures at the pre-crossover time points (ie, the range of multiple reported measurements between 1 day and 7 weeks post-treatment) ranged from 1.36 to 1.39 for HADS total score, from 0.80 to 1.18 for HADS-A, from 0.98 to 1.32 for HADS-D, from 0.82 to 1.10 for BDI, from 1.18 to 1.45 for STAI-State, and from 0.95 to 1.40 for STAI-Trait scores. Psilocybin was associated with sustained anxiolytic and anti-depressant benefits (based on 60–80% of participants with a continued clinically significant response) in the total cohort (ie, after psilocybin use by all participants) at follow-up after 6.5 months.

Limitations (per authors): Small study size; minimal racial/ethnic diversity of participants that is reflective of the cancer patient population; the interpretation of the results at the end of the study was limited by the crossover design; the control (niacin) had "limited blinding".

30. **Agin-Liebes GI, Malone T, Yalch MM, et al. Long-term follow-up of psilocybin-assisted psychotherapy for psychiatric and existential distress in patients with life-threatening cancer.** ***Journal of psychopharmacology.*** **2020;34(2):155-166.**

P: Remaining individuals with life-threatening cancer and psychiatric distress that were alive and completed the original trial reported by Ross et al. 2016. Compared to the original trial population, this subpopulation had a higher proportion of gynecological cancers (33%), and none had a diagnosis of digestive cancers (versus 21% in the full trial population). At the second long-term follow-up (LTFU), 71% of participants were in partial or complete remission from their cancer.

(Total *n* randomized = 29; and 16 were alive at follow-up, with n=15 agreeing to participate in this study).

I/C: All participants received 1 dose of oral psilocybin 0.3 mg/kg and therapy. See Ross et al. 2016.

O: Mean score on various anxiety or depression scales, including: (1) Hospital Anxiety and Depression Scale [HADS] total score; (2) patient-reported anxiety (HADS-A); (3) depression (HADS-D); (4) Beck Depression Inventory (BDI); and Spielberger State-Trait Anxiety Inventory (STAI), including (5) patient-reported levels of the anxiety state (STAI-S) and (6) trait (STAI-T).

T: The average first LTFU occurred at 3.2 years (range 2.3–4.5 years) and the average second LTFU was at 4.5 years (range 3.5–5.5 years) after the original psilocybin dosing date.

S: Long-term, uncontrolled, within-subject follow-up of a RCT (refer to Ross et al. 2016)

Primary conclusion(s): One dose of psilocybin was associated with statistically significant within-person reductions from baseline in anxiety and/or depressive symptoms for each of the 6 primary outcome measures at the first and second long-term follow-up. With respect to all 6 outcome measures the *mean* within-person effect size (Cohen's *d)* for the change from baseline to follow-up was 1.90 (range 1.27 to 2.67) at 6.5 months, 1.30 (range 0.93 to 1.97) at the first LTFU, and 1.41 (range 0.86 to 1.89) at the second LTFU.

Limitations (per authors): Due to the crossover design of the original RCT, there is not a control group for the long-term follow-up period, so any changes cannot be directly attributed to psilocybin; improvements in participant's cancer symptoms could have also improved their psychological status; small study size; minimal racial/ethnic diversity of participants limiting generalizability.

31. **Ross S, Agin-Liebes G, Lo S, et al. Acute and Sustained Reductions in Loss of Meaning and Suicidal Ideation Following Psilocybin-Assisted Psychotherapy for Psychiatric and Existential Distress in Life-Threatening Cancer. *ACS pharmacology & translational science.* 2021;4(2):553-562.**

NCT not reported, but it references including data from Ross et al. 2016 and Agin-Liebes et al. 2020.

This secondary analysis included a subset of the original trial population, and thus may not have maintained the full benefits of balanced randomization.

P: Adults (mean age of 60.3) with cancer (72.8% with stages III or IV) and an anxiety-related diagnosis of either adjustment disorder, depressed mood or generalized anxiety disorder *with baseline suicidal ideation (score >0)*.

(Total *n* randomized = 29; n = 11 included in this analysis, 6 from the psilocybin-first arm and 5 from the niacin-first arm).

I: Psilocybin-first: single dose of oral psilocybin (0.3 mg/kg) plus psychotherapy, followed by a single dose of oral niacin 250 mg plus psychotherapy 7 weeks later. Refer to Ross S et al. 2016.

C: Niacin-first: single dose of oral niacin 250 mg (active comparator) plus psychotherapy, followed by a single dose of psilocybin 0.3 mg/kg 7 weeks later. Refer to Ross et al. 2016.

O: Suicidal ideation composite score from baseline using a post-hoc generated score combining two items on the Beck Depression Inventory-II and the Brief Symptom Inventory questionnaires, and loss of meaning (LOM) score generated from 5 questions on the Demoralization Scale (DS) from baseline.

T: Suicidal ideation was measured at pre-crossover at 8 hours, 2 weeks, and 7 weeks after the first dosing session, and 6.5 months after the second dosing session. A composite suicidal ideation score was not created at the follow-up time points of 3.2 and 4.5 years. LOM was assessed pre-crossover at 2 weeks after the first dosing session, and post-crossover at 6.5 months, 3.2 years, and 4.5 years.

S: A post-hoc subgroup analysis of a randomized, double-blind, controlled, crossover study (Ross et al. 2016); and descriptive long-term follow-up study (pooling data from Agin-Liebes et al. 2020)

Primary conclusion(s): Among participants with a suicidal ideation score greater than 0 at baseline, the psilocybin arm showed statistically significant *within-group* reductions in suicidal ideation (SI) score

from baseline at 8 hours, 2 weeks, and 7 weeks after the first dosing session (P<0.05); however, there was not a statistically significant difference in SI score between the psilocybin-first and niacin-first arms from 8 hours to 7 weeks after the dosing session. The psilocybin-first LOM scores were statistically significantly lower than the niacin-first arm scores 2 weeks after the first dosing session (P=0.021). A statistically significant within-group (all participants after receiving psilocybin) benefit at 6.5 months relative to baseline was also observed for SI and LOM (P<0.001 for both outcomes). Significant reductions in LOM score at 3.2 and 4.5 years of follow-up relative to baseline were also observed for the entire cohort (P<0.001).

Limitations (per authors): The original trial was not designed to evaluate the effects of psilocybin on suicidal ideation in patients with cancer; the evaluation of long-term benefits is limited by the crossover design of the original trial due to a lack of a proper control group; minimal racial/ethnic diversity of participants limiting generalizability; an established measure for suicidal ideation would have improved interpretability rather than using a post-hoc generated composite score.

32. **Benville J, Agin-Liebes G, Roberts DE, et al. Effects of Psilocybin on Suicidal Ideation in Patients With Life-Threatening Cancer. *Biological Psychiatry.* 2021;89(9):S235-S236.**

NCT not reported, but it is described as a secondary analysis of a randomized, cross-over trial that appears to be the same trial reported by Ross et al. 2016.

Published as an abstract only. This abstract appears to be highly similar to the study by Ross et al. 2021 (citation #31). One difference is this abstract reports the outcome of desire for hastened death (DHD). Ross et al. 2021 considered DHD is be highly correlated with loss of meaning, the outcome reported by Ross et al. 2021.[76]

P: People with cancer and suicidal ideation at baseline
(Total *n* randomized = 29; *n* = 11 included in this analysis, 6 from the psilocybin-first arm and 5 from the niacin-first arm).

I: Psilocybin-first: single dose of oral psilocybin (0.3 mg/kg) plus psychotherapy with crossover to a single dose of oral niacin 250 mg plus psychotherapy 7 weeks later. Refer to Ross S et al. 2016.

C: Niacin-first: single dose of oral niacin 250 mg (active comparator) plus psychotherapy with crossover to a single dose of psilocybin 0.3 mg/kg 7 weeks later. Refer to Ross et al. 2016.

O: Changes in desire for hastened death (DHD), a score generated from two items on the Demoralization Scale.

T: Assessed at three pre-crossover timepoints, and several post-crossover timepoints, including at the 6.5 month timepoint, but exact outcome measurement times other than 6.5 months are not reported.

S: Secondary analysis of a randomized, double-blind, controlled, crossover study. Analysis performed per randomized group (ie, psilocybin vs niacin), but it was restricted to a subgroup of patients reporting suicidal ideation at baseline.

Primary conclusion(s): A statistically significant reduction in DHD was observed after psilocybin treatment (prior to crossover; P<0.01). For three post-crossover timepoints, the entire cohort of psilocybin-treated participants demonstrated significant decreases in DHD relative to baseline (P<0.005).

Limitations (per authors): Not reported

3.2.4.2.3 Citations addressing the original pilot trial: Grob et al. 2011 (NCT00302744)

33. **Grob CS, Danforth AL, Chopra GS, et al. Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. *Archives of general psychiatry.* 2011;68(1):71-78.**

P: Adults (ages 36 to 58 years) with advanced-stage non-brain cancer and reactive anxiety (ie, acute distress disorder, anxiety disorder due to cancer, adjustment disorder with anxiety).
(Total *n* randomized = 12)

I: One moderate oral psilocybin dose (0.2 mg/kg) was administered in one of two 6-hour sessions spaced several weeks apart, which started the morning after entering the hospital treatment facility. During the other session, participants received niacin. Participants were allowed to discuss subjective aesthetic, cognitive, affective, and psychospiritual experiences with study personnel after each session.

C: Oral niacin 250 mg, masked to match the intervention, administered during an intervention session that matched the psilocybin arm. During the other session, participants received psilocybin.

O: No primary outcome was specified; psychological measures included changes and differences in changes from baseline 5-Dimension Altered States of Consciousness (5D-ASC), Beck Depression Inventory (BDI), Profile of Mood States (POMS), State-Trait Anxiety Inventory (STAI), and Brief Psychiatric Rating Scale (BPRS). Safety outcomes were blood pressure, heart rate, and arrhythmias.

T: Outcomes measured the day before, the day after, and 2 weeks after each session, and then at monthly intervals for 6 months.

S: Randomized, double-blind (participants + staff), single-site (US), active placebo-controlled, within-participant (ie, patients were their own control) pilot trial. The order of receiving the interventions (psilocybin-first or niacin-first) was randomized, and each patient served as their own control.

Primary conclusion(s): Significant between-group differences in improvement from baseline were observed for psilocybin versus control within the oceanic boundlessness (P<0.001), visionary destructuralization (P<0.001), anxious ego dissolution (P=0.049), and auditory alterations (P=0.03) domains of 5D-ACS at unspecified time points using 1-way ANOVA. Differences from baseline BDI reached significance at 6 months (P=0.03), many months after all patients had received both treatment sessions. Similarly, significant differences from baseline STAI-Trait (but not STAI-state) scores were observed at 1 month (P=0.001) and 3 months (P=0.03) after the second session, when all participants had received psilocybin. Nevertheless, authors reported non-significant "trends" for a reduction in POMS and BDI scores from baseline to 2 weeks after psilocybin treatment that was not observed with niacin. Psilocybin was associated with a small statistically significant elevation in heart rate (P=0.03), systolic blood pressure (P<0.001), and diastolic blood pressure (P=0.03) versus control.

Limitations (per authors): Subjects and staff were consistently able to unmask randomized treatments; variable number of contacts with staff; many comparisons were made without differentiating between subjects who had versus had not yet received the intervention previously (ie, each patient's outcomes following the intervention were compared to the same measures following the control, regardless the ordering of those sessions), and pilot study with small sample size[‡‡]

3.2.4.3 Psilocybin for Alcohol Use Disorder

34. Amegadzie S, Mennenga S, Podrebarac S, Duane H, Ross S, Bogenschutz M. Psilocybin-assisted treatment for alcohol use disorder: A clinical perspective. *American Journal on Addictions.* 2018;27(4):317.

NCT not reported.

This is published as an abstract, so we were unable to verify all inclusion criteria. Bogenschutz et al. 2018[77] may be a full-text for this abstract. The investigators mentioned designing ***this ongoing trial*** *using*

[‡‡] Limitation(s) added by writers of this report that were not reported by investigators in the publication.

results of a single-arm (uncontrolled) clinical trial of psilocybin for alcohol use disorder by Bogenshutz et al. 2015[78] (NCT02061293).

P: People with alcohol use disorder (target enrolled *n* = 180)
I: Psilocybin-assisted therapy, 2-3 sessions. Therapy is Motivational Enhancement and Taking Action (META) therapy, including preparatory, experimental drug-administration, and debrief sessions.
C: Active-control containing diphenhydramine with therapy matching the psilocybin arm.
O: Not specified
T: Not specified, but the trial is planning for a 42 week treatment course
S: Descriptive study of an *ongoing (*ie, incomplete at the time of publishing this abstract) double-blinded, controlled trial.
Primary result(s): Describes experiences from 3 participants in the trial (this is descriptive, and inferences about the possible role of psilocybin cannot be made). Positive experiences were reported including reduced heavy drinking and alcohol abstinence in 2/3 participants.
Limitations (per authors): Preliminary descriptive data that precludes inferences about the efficacy of psilocybin for alcohol use disorder.

3.2.5 LSD Studies

3.2.5.1 LSD for Anxiety Associated with Life-Threatening Illness

3.2.5.1.1 Citations addressing the original phase 2 trial: Gasser et al. 2014 (NCT00920387)

35. Gasser P, Holstein D, Michel Y, et al. Safety and efficacy of lysergic acid diethylamide-assisted psychotherapy for anxiety associated with life-threatening diseases. *The Journal of nervous and mental disease.* 2014;202(7):513-520.

P: Adults with anxiety (STAI trait- or state-scale score ≥ 40) related to life-threatening disease. Half of participants also met criteria for generalized anxiety disorder. Participants discontinued depression and anxiety treatments before the start of the trial.
(Total *n* randomized = 12; 11 received the intervention)
I: Two psychotherapy-assisted administration sessions of 200 mcg of LSD separated from one another by 2-3 weeks in addition to ongoing drug-free psychotherapy sessions including 3 drug-free psychotherapy sessions lasting 60-90 minutes after each administration session.
C: Two psychotherapy-assisted sessions of 20 mcg LSD (active placebo) separated by 2-3 weeks with 3 drug-free psychotherapy sessions after each administration session.
O: Change in self-reported anxiety symptoms (STAI Form X)
T: Outcome measurements were completed at baseline, 1 week after each LSD-assisted session, and 2 and 12 months after completion of the last LSD-assisted session.
S: Phase 2, randomized (2 LSD 200 mcg: 1 LSD 20 mcg), double-blind, active placebo-controlled, pilot trial. After unmasking, there was an optional open-label crossover period where control participants received 2 LSD (200 mcg)-assisted therapy sessions plus 5 non-drug therapy sessions.
Primary Conclusions: STAI-*state* scores significantly decreased from baseline to 2 months after the 2nd LSD session for active-dose LSD-treated participants compared to control participants (mean [SD] STAI-state score at baseline: LSD 200 mcg, 53.1 [4.7] vs control, 47.7 [7.7]; mean [SD] STAI-state score at 2-month follow-up: LSD 200 mcg, 41.5 [3.2] vs control, 51.7 [5.3]; P = 0.021 for between group difference; effect size [Cohen's *d*] = 1.2). There were numerical decreases in STAI-*trait* scores

between baseline and 2 months after the 2nd LSD session for LSD compared to control; however, this was not statistically significant at the multiplicity-adjusted alpha threshold of 0.025 (mean [SD] STAI-trait score at baseline: LSD 200 mcg, 53.2 [4.3] vs control, 43.3 [7.0]; mean [SD] STAI-state score at 2-month follow-up: LSD 200 mcg, 45.2 [3.7] vs control, 49.0 [6.1]; P = 0.033 for between group difference; effect size [Cohen's *d*] = 1.1). Anxiety symptom changes were sustained at 12 months in the overall cohort (ie, after LSD 200 mcg-assisted therapy for all participants). No severe LSD-related AE were reported. In general, a greater variety and higher overall incidence of AE were reported for the LSD 200 mcg arm, but the majority of events were transient, occurring within 1 day of receipt of LSD.

Limitations (per authors): Small sample size; blinding was insufficient as nearly all participants and therapists successfully identified the group assignment; inability to account for the possible psychological impact of changes in the participants life-threatening disease; assessed quality-of-life secondary outcome measures are focused on physical but not psychological changes.

36. Gasser P, Kirchner K, Passie T. LSD-assisted psychotherapy for anxiety associated with a life-threatening disease: a qualitative study of acute and sustained subjective effects. *Journal of psychopharmacology.* 2015;29(1):57-68.

P: Adults with anxiety symptoms associated with life-threatening illness, refer to Gasser et al. 2014. (*n*=12 participants completed the original trial, and *n*=10 entered the long-term follow-up [LTFU] period; data for 9 participants was included for the STAI analysis and audio recording).

I/C: See Gasser et al. 2014**.** Control participants that did not opt to crossover to the 200 mcg LSD dose after completion of initial study were not eligible for LTFU.

O: Change in self-reported anxiety symptoms (per Spielberger STAI Form X)

T: LTFU, 12 months after last administration of 200 mcg LSD dose

S: Open-label, single-arm LTFU of phase 2 randomized, active-controlled pilot trial, including a qualitative content analysis via semi-structured interviews of participants.

Primary Conclusions: In the total cohort of participants that received 2 LSD (200 mcg)-assisted sessions, there were statistically significant reductions between baseline and 12-months for the mean STAI State score (P=0.0005) and STAI Trait score (p=0.004). Interviewed participants exhibited a positive impression of LSD-assisted therapy: "…participants consistently reported insightful, cathartic and interpersonal experiences, accompanied by a reduction in anxiety (77.8%) and a rise in quality of life (66.7%)."[79] Investigators speculate at the potential therapeutic mechanism for LSD-assisted therapy. Participants did not any report adverse events during the extended follow-up.

Limitations (per authors): Refer to limitations mentioned by Gasser et al. 2014; at LTFU, only a subset of the original trial cohort was included; a control group for LTFU was lacking due to cross-over of the control group during the original trial.

3.2.5.2 Other LSD Citations

37. Liechti ME, Holze F, Vizeli P, Schmid Y. Acute effects of LSD in healthy subjects and in patients during LSD-assisted psychotherapy. *Psychotherapy and Psychosomatics.* 2019;88:75.

NCT not reported

Published as an abstract only, so we are unable to fully confirm that this study meets inclusion criteria.

P: Mix of participants considered healthy and affected by a psychiatric disorder (Total *n* unclear; the abstract mentions 40 healthy participants, 8 patients with varying unspecified, psychiatric conditions, and 11 patients with life-threatening illness-associated anxiety).

I: LSD 0.1 to 0.2 mg

C: Placebo

O: Changes in visual analog scale scores on the 5-dimensions of Altered States of Consciousness (5D-ASC) scale scores, and mystical experience questionnaire (MEQ)

T: Unspecified, "acute effects"

S: Unclear; appears to be a pooled secondary analysis from 2-3 clinical trials/studies: 1 double-blinded, placebo-controlled cross-over trial of healthy participants; 1 placebo-controlled trial of people with anxiety associated with life-threatening illness; and another of patients treated in psychiatric practices.

Primary conclusion(s): LSD-associated effects measured on the 5D-ASC and MEQ were similar between healthy participants and patients with psychiatric conditions. Among the healthy participants, dose-dependent LSD-associated changes included increased feelings of openness, trust, and closeness; and on the 5D-ASC, increased bliss, insightfulness, and "…changed meaning of percepts"[80] compared to placebo.

Limitations (per authors): Not reported; information reported in the abstract is insufficient to determine whether all comparisons were versus placebo[§§]

3.2.6 Ayahuasca Studies

3.2.6.1 Ayahuasca for Major Depressive Disorder

3.2.6.1.1 Citations addressing the clinical trial: Palhano-Fontes et al. 2019 (NCT02914769)

38. Palhano-Fontes F, Barreto D, Onias H, et al. Rapid antidepressant effects of the psychedelic ayahuasca in treatment-resistant depression: a randomized placebo-controlled trial. *Psychological medicine.* 2019;49(4):655-663.

P: Adults (18-60 years) with treatment-resistant (failure of at least 2 different prior medications) moderate-to-severe (HAM-D score ≥ 17) unipolar major depression. People with prior exposure to ayahuasca were excluded.
(Total *n* randomized = 35, and 29 were analyzed)

I: Ayahuasca 1 ml/kg made from a single brew (dose of 0.36 mg/kg of N,N-DMT) x 1 dose. Given during an 8-hour session coupled with relaxing music and support of 2 investigators in the next room.

C: Matched (color and contained zinc to stimulate some gastrointestinal distress) liquid placebo 1 ml/kg x 1 dose. Given during an 8-hour dosing session coupled with relaxing music and support of 2 investigators in the next room.

O: Change in depression severity (on the Hamilton Depression Rating Scale [HAM-D]) from baseline; a secondary outcome was change in Montgomery-Åsberg Depression Rating Scale (MADRS) scores from baseline

T: HAM-D was measured 7 days after the intervention, and MADRS was measured 1, 2, and 7 days after the dose.

S: Randomized (1:1), double-blind, parallel-group, placebo-controlled single-site (Brazil) trial

Primary conclusion(s): Ayahuasca-treated participants experienced a significantly larger decrease in mean HAM-D scores between baseline and 7-days post-dose compared to the placebo-treated participants (P=0.019; effect size [Cohens *d*]=0.98). Significant differences in mean MADRS score between the ayahuasca and the placebo arm were observed at day 1, day 2, and day 7 after dosing.

[§§] Limitation(s) added by writers of this report that were not reported by investigators in the publication.

At day 7 post-dose, 64% of the ayahuasca arm compared to 27% of the placebo arm were treatment responders.

Limitations (per authors): Small sample size; low generalizability to patients with depression not well represented in the study (patients had treatment-resistant depression with a high comorbidity of a personality disorder); possibility of unmasking interventions. Investigators report taking steps to reduce the possibility of patients or investigators predicting assigned treatments.

39. **Galvão-Coelho NL, de Menezes Galvão AC, de Almeida RN, et al. Changes in inflammatory biomarkers are related to the antidepressant effects of Ayahuasca.** ***Journal of Psychopharmacology.*** **2020;34(10):1125-1133.**

The methods of this article are poorly reported. It seems that they randomized people with or without depression 1:1 to ayahuasca or placebo control, but we are not sure that they stratified by depression diagnosis to achieve a balance between the ayahuasca and control group. The primary exposure reported in this article is depression status.

P: Refer to Palhano-Fontes et al. 2019. This additional analysis included both adults without any psychiatric condition (n=45) and adults with treatment-resistant major depression not taking any antidepressants (N=28; ayahuasca (N=14), placebo (N=14)).

I: Ayahuasca 1 ml/kg made from a single brew (dose of 0.36 mg/kg of N,N-DMT) x 1 dose. Given during an 8-hour dosing session coupled with relaxing music and support of 2 investigators in the next room.

C: Matched (color and contained zinc to stimulate some gastrointestinal distress) liquid placebo 1 ml/kg x 1 dose. Given during an 8-hour dosing session coupled with relaxing music and support of 2 investigators in the next room.

O: The primary outcome is unclear. Acute changes in blood inflammatory biomarkers (C-reactive protein [CRP] and interleukin [IL]-6) were measured. Additionally, the potential correlation between the inflammatory biomarkers and serum cortisol and serum brain-derived neurotrophic factor (BDNF) was assessed.

T: Timing of biomarker measurement is not explicitly reported. It appears they were measured at baseline pre-treatment (D0-p), and 48 hours after the dosing session (D2).

S: Exploratory analysis of a randomized (1:1), double-blind, parallel-group, placebo-controlled single-site (Brazil) trial

Primary conclusion(s): Pre-treatment baseline CRP levels were significantly inversely correlated with cortisol levels among people with depression (*Spearman rho =* –0.40; P=0.033), but were not significantly correlated among people without depression (P=0.28). Among people with depression, reduced CRP levels from baseline to D2 correlated with a lower MADRS score 48 hours after the intervention among ayahuasca recipients (P=0.003 for change in MADRS score from baseline; *Spearman's rho* for correlation=0.57, P≤ 0.050), but not placebo recipients (P>0.050 for *Spearman's rho)*. No significant correlations between treatment arm (ayahuasca vs placebo) and change in IL-6 levels were observed among people with depression.

Limitations (per authors): Use of total BDNF instead of pro-/mature BDNF concentrations; small sample size; population of people with depression is limited to treatment-resistant patients and many of them also had comorbid conditions including an anxiety or personality disorder; limited by use a single treatment with a limited number of blood samples on a given day

40. **de Almeida RN, Galvao ACdM, da Silva FS, et al. Modulation of Serum Brain-Derived Neurotrophic Factor by a Single Dose of Ayahuasca: Observation From a Randomized Controlled Trial.** ***Frontiers in psychology.*** **2019;10(101550902):1234.**

The methods of this article are poorly reported. It seems that they randomized people with or without depression 1:1 to ayahuasca or placebo control, but we are not sure that they stratified by depression diagnosis to achieve a balance between the ayahuasca and control group. The primary exposure reported in this article is depression status.

P: Refer to Palhano-Fontes et al. 2019. This additional analysis included both adults without depression (n=45) and adults with treatment-resistant major depression not taking any antidepressants (N=28; ayahuasca (N=14), placebo (N=14)). People with hypercortisolemia at baseline were excluded from the analysis (4 patients in the healthy population).

I: Ayahuasca 1 ml/kg made from a single brew (dose of 0.36 mg/kg of N,N-DMT) x 1 dose. Given during an 8-hour dosing session coupled with relaxing music and support of 2 investigators in the next room.

C: Matched (color and contained zinc to stimulate some gastrointestinal distress) liquid placebo 1 ml/kg x 1 dose. Given during an 8-hour dosing session coupled with relaxing music and support of 2 investigators in the next room.

O: The primary outcome is unclear. Acute changes in serum brain-derived neurotrophic factor (BDNF) levels from baseline were measured. Predictors of baseline serum BDNF were assessed in a multiple linear regression model. Additionally, changes in BDNF before and after treatment (ayahuasca or placebo) was assessed in a general linear model. A logistic regression model was used to assess depression remission (MADRS score ≤10).

T: BDNF and depression severity (MADRS total score) were assessed at baseline before receipt of treatment (D0) and 48 hours after treatment (D2).

S: Randomized (1:1), double-blind, parallel-group, placebo-controlled single-site (Brazil) trial

Primary conclusion(s): Among people with depression at baseline, BDNF levels 48 hours after treatment were significantly negatively correlated with MADRS score among people receiving ayahuasca (*Spearman rho = –0.55;* P≤0.05) but not placebo (*Spearman rho =* –0.27; P>0.05). Post-treatment BDNF levels were higher among people with or without depression that received ayahuasca compared to those receiving placebo (P = 0.03); a between-group difference that was not present at baseline. The authors hypothesize that ayahuasca-induced changes in BDNF may modulate anti-depressant effects.

Limitations (per authors): Not reported. Refer to Palhano-Fontes et al. 2019. Note that this is a small sample size and it unknown whether authors adjusted for multiple statistical comparisons[***].

41. Zeifman RJ, Palhano-Fontes F, Hallak J, Arcoverde E, Maia-Oliveira JP, Araujo DB. The impact of ayahuasca on suicidality: Results from a randomized controlled trial. *Frontiers in Pharmacology.* 2019;10.

P: Adults with unipolar treatment-resistant (insufficient response to 2+ antidepressants) MDD that discontinued antidepressants prior to the trial.
(Total *n* = 29)

I/C: Refer to Palhano-Fontes et al. 2019; single-dose of ayahuasca versus placebo

O: Between-group and within-group effect sizes (Cohen's *d)* for the change from baseline in mean MADRS-suicidality item score (item 10 rated from 0 to maximum of 6; significant suicidality considered a score ≥ 4) using a fixed-effect linear mixed model controlled for baseline MADRS-suicidality item score

T: Measured at baseline and after (1 day, 2 days, and 7 days) the intervention

S: Secondary analysis of a randomized (1:1), double-blind, parallel-group, placebo-controlled single-site (Brazil) trial.

[***] Limitation(s) added by writers of this report that were not reported by investigators in the publication.

Primary conclusion(s): The effect size (*d;* 95% confidence interval) for between-group (ie, ayahuasca versus placebo) changes in suicidality was moderate-sized at day 1 (0.58; –1.32 to 0.17), day 2 (0.56; –1.30 to 0.18) and day 7 (0.67; –1.42 to 0.08) after the receipt of study intervention. The effect size for within-group (ayahuasca recipients) decreases in suicidality compared to baseline were 1.33, 1.42, and 1.19 at 1 day, 2 days, and 7 days after treatment, respectively. The overall effect for change in suicidality for ayahuasca versus placebo in the linear mixed model was not statistically significant (P=0.088); the effect of time, but not the time-intervention interaction, was statistically significant (P<0.05).

Limitations (per authors): Lower baseline suicidality scores in the placebo arm, which the investigators tried to control for in the analysis; small study size; low generalizability to people with an immediate risk of suicide; lack of qualitative analysis to improve the understanding of the observed ayahuasca-associated effects; possibility that participants were able to identify which treatment they received.

42. Galvão ACM, de Almeida RN, Silva EAS, et al. Cortisol modulation by ayahuasca in patients with treatment resistant depression and healthy controls. *Frontiers in Psychiatry.* 2018;9.

The methods of this article are poorly reported. It seems that they randomized people with or without depression 1:1 to ayahuasca or placebo control, but we are not sure that they stratified by depression diagnosis to achieve a balance between the ayahuasca and control group. The primary exposure reported in this article is depression status.

P: See Palhano-Fontes et al. 2019. This additional analysis included both adults without depression (n=43) and adults with treatment-resistant major depression not taking any antidepressants (N=28; ayahuasca (N=14), placebo (N=14)). People with hypercortisolemia at baseline were excluded from the analysis (4 patients in the healthy population).

I: Ayahuasca 1 ml/kg made from a single brew (dose of 0.36 mg/kg of N,N-DMT) x 1 dose. Given during an 8-hour dosing session coupled with relaxing music and support of 2 investigators in the next room.

C: Matched (color and contained zinc to stimulate some gastrointestinal distress) liquid placebo 1 ml/kg x 1 dose. Given during an 8-hour dosing session coupled with relaxing music and support of 2 investigators in the next room.

O: The primary outcome is unclear. Acute changes in plasma and awakening salivary cortisol response were measured. Normalized area under the curve (AUC) values for salivary and plasma cortisol, and spearman correlations were calculated.

T: Plasma and awakening (participants slept inpatient the night before) salivary cortisol were measured at baseline pre-treatment (D0-p), during the dosing session (D0-t, about 1 hour and 40 minutes after the dose), and 48 hours after the dosing session (D2).

S: *Exploratory* analysis of a randomized (1:1), double-blind, parallel-group, placebo-controlled single-site (Brazil) trial

Primary conclusion(s): At baseline, after adjustment for sex, people with depression had a lower salivary cortisol response and lower plasma cortisol level relative to healthy participants. Among people with depression at baseline, salivary cortisol increased significantly (P=0.03) more during the ayahuasca dosing session (median % change = 98.72; 25th to 75th quartile=37.89 to 177.16) compared to placebo (median % change = 23.26; 25th to 75th quartile= –5.44 to 41.65). Similar during treatment changes were observed among healthy participants that received ayahuasca relative to placebo. The authors hypothesized that ayahuasca may acutely change salivary cortisol levels.

Limitations (per authors): Not reported. Refer to Palhano-Fontes et al. 2019. Note that this is a small sample size, and it unknown whether authors adjusted for multiple statistical comparisons[†††].

3.2.7 Ibogaine Studies

3.2.7.1 (Nor)Ibogaine for Management of Opioid Withdrawal

43. Glue P, Cape G, Tunnicliff D, et al. Ascending Single-Dose, Double-Blind, Placebo-Controlled Safety Study of Noribogaine in Opioid-Dependent Patients. *Clinical pharmacology in drug development.* 2016;5(6):460-468.

NCT not reported. The Australian New Zealand Clinical Trial Registry number is ACTRN12613001064796.

P: Adults ages ≥ 18 years discontinuing established methadone opioid substitution therapy (OST) at a dose between 25-80 mg/day, within 7 days after switching to morphine controlled-release x 6 days and immediate release x 1 day
(Total *n* randomized = 57)

I: One of 3 oral noribogaine doses (60, 120, or 180 mg) administered after fasting ≥10 hours and 24 hours after beginning a 72-hour onsite monitoring session

C: Matching placebo administered in onsite session matching the intervention arm

O: No primary outcome was specified; efficacy outcomes were mu-opioid agonist sensitivity, withdrawal (including pupillometry, oximetry, and capnography, time to OST resumption, and opioid withdrawal symptoms using Clinical, Objective and Subjective Opioid Withdrawal Scales [COWS, OOWS, and SOWS]); safety outcomes were change in QTc interval, visual impairment, headache, and nausea

T: All outcomes assessed within 0 to 216 hours after treatment

S: Randomized (2:2:2:1), double-blind, placebo-controlled, parallel-group, single-site (US) trial

Primary conclusion(s): Significant dose- and concentration-dependent increases in the QTC interval (P-values not reported); magnitude of QTc interval prolongation was clinically meaningful with higher noribogaine doses. Mild and transient adverse effects were common and included visual impairment, headache, and nausea. No significant differences in time-to-resumption of OST or opioid withdrawal symptoms for ibogaine versus placebo; mean (SD) time was 8.6 (3.7), 22.5 (10.3), 11.4 (5.0) and 13.9 (7.4) hours for 60 mg, 120 mg, 180 mg, and placebo, respectively.

Limitations (per authors): This was a single-dose study, but repeated dosing may be required to achieve prolonged withdrawal symptom reduction; study was underpowered for most outcomes.

3.3 Other Noted References or Resources of interest

During this preliminary literature review, we noted some references that may be of additional interest to the Task Force.

3.3.1 Selected Trials Excluded During Screening

Results of a single-arm open-label 14 participant trial of MDMA-assisted therapy (187.5 mg for 2 sessions) for **alcohol use disorder** have been published. Authors concluded this is preliminary evidence of tolerability in this population.[81]

[†††] Limitation(s) added by writers of this report that were not reported by investigators in the publication.

3.3.1.1 Studies addressing Microdoses of Psychotherapy drugs

There is growing interest in the potential use of smaller than standard hallucinogenic doses (eg, 5-10% of total standard dose every 3 days) of target psychotherapy drugs to achieve improved mental health outcomes.[82] Two experimental trials excluded in the full-text review (Marschall et al. 2022[82] and Szigeti et al. 2021[83]) evaluated use of microdoses of one or more psychotherapy drugs, but were excluded from the annotated bibliography owing to enrollment of all or primarily healthy participants. Four additional healthy volunteer placebo-controlled clinical trial references (some that might be from the same trial) excluded during the title/abstract review evaluated the impact of microdoses of LSD on cognitive and mood outcomes,[84,85] functional connectivity and cerebral blood flow,[86] or the association between subjective LSD affects and negative emotionality.[87]

3.3.2 Public Health Vision and/or Barriers to Widespread use of Psychedelic Agents

Williams et al. 2021[88] and Haden et al. 2016[13] describe barriers and potential solutions to address challenges in the use of psychedelic agents from the perspective of Canada and Australia, respectively. Some of these concerns and solutions may be applicable in the US. Marks and Cohen 2021[89] also briefly describe barriers in the US.

3.3.3 Societal Impact

Nutt et al. 2010[90] published a United Kingdom-based drug harm decision analysis, which provides a framework for categorizing potential harms to self and society associated with various drugs.

3.3.4 Therapy Model and/or Training of Therapists

- The manual and/or supportive information from the Multidisciplinary Association for Psychedelic Studies (MAPS) about the therapeutic model and therapist training to provide MDMA-assisted psychotherapy for PTSD is available at: https://mapspublicbenefit.com/training/
- The MAPS manual for MDMA-assisted therapy for treatment of anxiety associated with life-threatening illness (used by the Wolfson et al. 2020 phase 2 trial[91]) is available: https://s3-us-west-1.amazonaws.com/mapscontent/research-archive/mdma/mda1/MAPS_MDMA_MDA1_Treatment_Manual.pdf
- Tai et al. 2021[92] address the therapeutic model and therapist training for psilocybin-assisted treatment of depression (from the COMPASS Pathways group)
- Post-graduate certificate programs with training to provide psychedelic-assisted therapy: https://www.ciis.edu/research-centers/center-for-psychedelic-therapies-and-research/about-the-certificate-in-psychedelic-assisted-therapies-and-research, https://www.fluencetraining.com/certificates/postgraduate-certificate-in-psychedelic-integration-therapy/ .
- ICEERS (The International Center for Ethnobotanical Education, Research and Service) created an online course for crisis support training for health care professionals: https://www.iceers.org/e-course-integration-crisis-support/

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APPENDIX A – PROPOSED PHARMACOLOGY, HISTORICAL DOSES, AND HISTORICAL SAFETY INFORMATION FOR TARGET PSYCHOTHERAPY DRUGS

Table A1. Background Information on the Proposed Pharmacology, Historical dose and dosage forms, and Safety Information of Psychotherapy Drugs

***Proposed* Pharmacology[a]**	**Common formulations and historical route of ingestion[b]**	**Preliminary Safety Information[c]**
"Classical" psychedelics		
LSD (D-lysergic acid diethylamide)		

Primarily[93]:
• Potent 5-HT $_{2A}$ partial receptor agonist
• Increases excitability and functional connectivity in thalamic and cortical regions within the brain
• Promotes glutamate release from the frontal cortex
Secondarily[93,94]:
• Also interacts with 5-HT $_{1A}$, 5-HT $_{2C}$, 5-HT $_{2B}$
• Binds to D_2 receptors
• Elevates ACTH and cortisol concentrations
	Traditional dosage forms:
	Most common [95,96]: Small square blotter papers soaked in LSD
	Other forms[97]:
	• Tablets ("microdots")
	• Capsules
	• Liquid (clear)
	• Gelatin squares ("window panes")
	
	Consumed **orally** by swallowing or absorbed through the tissues within the mouth
	
	Dose:
	• Usual hallucinogenic dose[d]: 20—80 µg[98]
	• Typical non-therapeutic (ie, recreational) dose[e]: 20—30 µg[99]
		Short-term AEs[97,98,100,101]:
		• Inability to recognize reality (derealization) and think logically
		• Depersonalization
		• Visual hallucinations
		• Synesthesia
		• Rapid and impulsive emotional changes
		• Hypertension, elevated heart rate, hyperthermia
		• Dizziness
		• Sweating
		• Loss of appetite or dry mouth
		• Tremors, numbness, weakness
		• Mydriasis
		Long-term AEs[97,101]:
		• **HPPD** (unpleasant flashbacks)
		  ○ Visual disturbances (eg, halos or trails surrounding moving objects)
		• **Persistent psychosis**
		  ○ Persistent visual hallucinations
		  ○ Paranoia
		  ○ Disorganized thinking
		  ○ Mood swings
		SAEs (rare) with doses > 400 µg[98]:
		• Coagulopathy

Table A1. Background Information on the Proposed Pharmacology, Historical dose and dosage forms, and Safety Information of Psychotherapy Drugs

***Proposed* Pharmacology[a]**	**Common formulations and historical route of ingestion[b]**	**Preliminary Safety Information[c]**
		• Seizures • Coma • Respiratory arrest **Dependence potential**: Low[14] **Tolerance:** Known to develop with repeated use[95,102] **Withdrawal symptoms:** Unknown
Psilocybin[c] [103](4-phosphoryloxy-N,N-dimethyltryptamine)		
Metabolized to psilocin (*active compound*) Primarily:[93] • 5-HT_{2A} partial receptor agonist Secondarily:[93,94] • Also interacts with 5-HT_{1A}, 5-HT_{2C}, 5-HT_{2B} • Elevated ACTH and cortisol concentrations	**Traditional dosage forms:** Fresh or dried mushrooms[97] Consumed orally by swallowing (eaten, brewed, mixed with other foods to mask bitterness)[96,97] **Dose:** • Usual hallucinogenic dose[d]: 4—6 mg of psilocybin or 5—100 mushrooms[98] • Typical recreational dose[e]: 10—50 mg (20—30 g fresh mushrooms or 1—2 g of dried mushroom powder)[98]	**Short-term AEs[97,101]:** • Feelings of relaxation • Visual hallucinations • Inability to recognize reality (derealization) • Altered perception of time • Panic, nervousness, paranoia • Mydriasis • Nausea, vomiting • Drowsiness **Long-term AEs[97]:** • Memory issues • Risk of flashbacks **SAEs (rare)[98,103]:** • Acute kidney failure • Seizures • Encephalopathy • Rhabdomyolysis **Dependence potential**: Low[14] **Cross-tolerance:** Known cross-tolerance exists between psilocybin and other "classic" psychedelics (LSD, mescaline)[14] **Withdrawal symptoms:[97,103]** Mixed evidence suggests unknown or none

Table A1. Background Information on the Proposed Pharmacology, Historical dose and dosage forms, and Safety Information of Psychotherapy Drugs

***Proposed* Pharmacology[a]**	**Common formulations and historical route of ingestion[b]**	**Preliminary Safety Information[c]**
		Other concerns[97,101]: Risk of poisoning (from accidental consumption of toxic mushrooms)
Ayahuasca (usually contains DMT in addition to other compounds)		
B-carboline alkaloids (eg, from the vine *Banisteriopsis caapi)* inhibit MAO-A, preventing metabolism of **DMT** *(*psychoactive ingredient from the plant *Psychotria viridis)* in the digestive tract[93] (*refer to DMT*) Harmines may also have psychoactive activity, so the cumulative effects from ayahuasca may depend on the unique mixture[8]	**Traditional dosage forms:** **Tea**: brewed from a mixture of plants, typically *Banisteriopsis caapi* and *Psychotria viridis*[97] Consumed **orally** **Dose:** • Varies based on the plants • Estimated harmine dose needed for oral DMT activity: 1-2 mg/kg[8] • Estimated **oral** dose range for DMT co-administered with harmines: 0.5 mg/kg to 1 mg/kg[8]	**Short-term AEs[97,101]:** • Altered visual and auditory hallucinations • Elevated heart rate • Hypertension • Nausea, vomiting • Burning stomach sensation • Heightened skin sensitivity and tingling sensations **Long-term AEs[97]:** • May alter the serotoninergic and immune systems, but further investigation is needed **SAEs (rare)[104]:** • Seizures • Psychosis • Coma **Dependence potential**: Unknown[97] **Tolerance:** None[14] **Withdrawal symptoms:** Unknown[97]
DMT[c] (N,N-dimethyltryptamine)		
• 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, and 5-HT_{2B} receptor agonist[93] • 5-HT and NE transporter inhibitor[6]	**Traditional dosage form:** Yellow or white crystalline powder[97] May be **smoked** or **injected** (ie, when administered alone)[105] **Dose:** • Typical hallucinogenic dose[d]: 0.2 to 0.4 mg/kg IV[105]	**Short-term AEs[97,101]:** • Elevated heart rate • Hypertension • Agitation • Seizures • Mydriasis • Visual hallucinations that often include body and spatial distortions

Table A1. Background Information on the Proposed Pharmacology, Historical dose and dosage forms, and Safety Information of Psychotherapy Drugs

***Proposed* Pharmacology[a]**	**Common formulations and historical route of ingestion[b]**	**Preliminary Safety Information[c]**
		• Depersonalization • Auditory distortions **Long-term AEs:** Unknown[97] **SAEs (rare) at higher doses[97]:** • Heart and respiratory arrest **Dependence potential**: Unknown **Tolerance:** None[101,106] **Withdrawal symptoms:** Unknown[97]
Entactogens/"Empathogens"		
MDMA (3,4-methylenedioxymethamphetamine)		
Phenethylamine that is structurally similar to amphetamine and mescaline[93] Multiple proposed mechisms[93]: • 5-HT and NE transporter reuptake inhibitor • Monoamine release and monoamine oxidase inhibitor • 5-HT_{2A} and 5-HT_{1A}, and 5-HT_{2C} partial receptor agonist • Increase oxytocin levels in the blood	**Traditional dosage form:** **Most common[97,107]:** • Tablets (various colors with imprinted logos) • Capsules • Liquid **Other forms:** • Powder Ingested orally by swallowing or intranasally by snorting[108] **Dose:** • Usual hallucinogenic dose[d]: 50—200 mg[98] • Typical recreational dose[e]: 100—200 mg tablets[95]	**Short-term AEs[97]:** • Heighted sensory perception • Reduced inhibition • Hypertension, elevated heart rate • Muscle tightness • Nausea • Sweating or chills • Rapid increased in body temperature resulting in kidney failure or death **Long-term AEs[97]:** • Depression • Persistent confusion • Issues with attention, memory, and sleep • Anxiety, impulsiveness • Decreased libido **Dependence potential**: Uncertain but evidence seems to suggest a dependence potential[14,109] **Tolerance:** May develop with chronic use[110]

Table A1. Background Information on the Proposed Pharmacology, Historical dose and dosage forms, and Safety Information of Psychotherapy Drugs

***Proposed* Pharmacology[a]**	**Common formulations and historical route of ingestion[b]**	**Preliminary Safety Information[c]**
		Withdrawal symptoms[97]: • Loss of appetite • Depression • Fatigue • Difficulty concentrating
Atypical Psychedelics		
Ibogaine (10-methoxyobogamine)		

The primary receptor(s) responsible for ibogaine/metabolites effects is not known.[111] It has weak affinities at many receptors/transporters,[111] for example:
• *Kappa* opioid receptor partial agonist[111]
• *Mu* opioid receptor antagonist[111]
• α3β4 nicotinic receptor antagonist[111]
• Noncompetitive inhibitor at dopamine and 5-HT transporters[111]
• Also binds to serotonin (5-HT_2, 5-HT_3), muscarinic (M_1, M_2), and sigma-2 receptors[112]
The 12-hydroxy metabolite (noribogaine) possesses similar but different affinities.[111]
	Traditional dosage forms[112]:
	• Chewing bark of the *T. Iboga* plant
	• Tablets, tonics, and capsules have been used historically
	
	Dose[8]:
	• Historical dose when used for asthenia: 10-30 mg daily
	• Historical dose when used as a stimulant: ~8 mg
	• Dose for anti-addictive effects is unclear, but anecdotally, 10-20 mg/kg have been used[5]; doses >12 mg/kg are considered to carry increased cardiovascular risk
		Subjective acute effects[8,112]:
		• Visual, introspective "waking dreams" (oneiric effects)
		• Evaluative emotional state
		• Increased arousal or alertness
		
		Other short-term AE[112]:
		• Nausea
		• Mild tremor and ataxia
		
		Toxicity concerns:
		• Cardiovascular toxicity:
		  ○ Ibogaine may lower the heart rate, and prolongs the QTc interval, possibly in a dose-dependent manner[77]; deaths attributed to ibogaine-induced QT interval prolongation have occurred, possibly in non-controlled setttings[7]
		  ○ Hypotension[112]
		• Neurotoxicity:
		  ○ Destruction of cerebellar Purkinje cells at high doses in rats and rodents[111]
		  ○ Tremors, ataxia[112]
		  ○ Seizures at very high doses[111]

Table A1. Background Information on the Proposed Pharmacology, Historical dose and dosage forms, and Safety Information of Psychotherapy Drugs

***Proposed* Pharmacology[a]**	**Common formulations and historical route of ingestion[b]**	**Preliminary Safety Information[c]**
		• Ibogaine-associated deaths have been reported since 1990 (one report included 33 cases); in cases with sufficient information, most people were considered to have predisposing factors to toxicity including use of higher than recommended ibogaine doses, use of interacting medications, preexisting cardiovascular disease, or electrolyte disturbances. Further, the ibogaine product purity was often unknown.[7] **Other concerns:** • Metabolized by CYP2D6 (to form noribogaine) and may interact with other drugs metabolized by this enzyme; additionally, CYP2D6 exhibits polymorphic expression[112]

Abbreviations: 5-HT, serotonin; AE, adverse effects; ATCH, adrenocorticotropic hormone; CYP, cytochrome P450 enzyme; D, dopamine; DEA, United States Drug Enforcement Administration; DMT, N,N-dimethyltryptamine; g, grams; HPPD, Hallucinogen Persisting Perception Disorder; IV, intravenously; MAO, monoamine oxidase; NE, norepinephrine; SAEs, serious adverse effects; NMDA, N-methyl-D-aspartate;

Key:

[a] This is preliminary information from review articles or compendia that is not intended to be comprehensive.

[b] This historical information is primarily based on recreational, nontherapeutic use of the psychotherapy drugs. **This information should not be relied upon for forming recommendations for therapeutic use of these medications.**

[c] The potential side effects and safety information was compiled using various compendia, including the National Institute on Drug Abuse (for psychotherapy drugs other than ibogaine), among others. **Note that this safety information is preliminary, and may be on use of these drugs under widely varying conditions (eg, different doses, setting, use with other substances), and may or may not reflect expected effects when these substances are used in controlled, monitored settings.**

[d] The usual dose that an individual begins to experience psychotropic effects. **Dosage variations exist and should be interpreted with caution.**

[e] The usual dose used for non-therapeutic (ie, recreational) purposes. Dosage variations exist based on numerous variables (eg, preparation) and should be interpreted with caution

APPENDIX B – LITERATURE SEARCHES

Search 1: Ovid-Medline

Table B1. Ovid-Medline Search for Experimental Trials for Target Drug-Disease Pairs

Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to June 03, 2022

Search date: June 6, 2022

#	Search String	Results	Annotations
1	Anxiety/ or exp Anxiety Disorders/ or exp Stress, Psychological/	304551	
2	anxiet* or anxious or (affective adj (symptom* or disorder*)) or adjustment disorder* or (agoraphobi* or phobic or phobia or panic or obsessive or OCD or stress or neurosis or neuroses or neurotic or distress or GAD or psychoneuro*)).ti,ab,kw,kf.	1258076	
3	1 or 2	1343155	Anxiety indication
4	exp stress disorders, traumatic/ or (trauma* or posttrauma* or PTSD).ti,ab,kw,kf. or ((stress adj2 (syndrome or disorder)) or PTSS).ti,ab,kw,kf.	450298	PTSD indication
5	exp depression/ or exp Depressive Disorder/ or mood disorders/ or affective symptoms/	268677	
6	(((mood or mental or behavior*) adj2 disorder*) or (depressed or depressive? or depression or MDD or TRD or dysthymi*) or (affective adj2 (state* or symptom* or disorder*))).ti,ab,kw,kf.	579445	
7	5 or 6	633669	Depression indication
8	(methamphetamine* or substance or drug* or polydrug or cocaine or crack or nicotine or tobacco).ti,ab,kw,kf. or exp amphetamine/ or exp cocaine/ or exp smoking/ or exp smoking cessation/ or exp nicotine/	2300392	
9	(abstin* or abstain* or abuse* or addict* or dependen* or misus* or overdose or withdrawal* or disorder* or cess*).ti,ab,kw,kf.	3408478	
10	8 and 9	484784	
11	(alcohol* and (abuse* or abstin* or abus* or addict* or consum* or dependen* or disorder* or drink* or excess* or misus* or problem* or risk* or withdrawal* or treatment or cess*)).ti,ab,kw,kf.	237804	
12	exp substance-related disorders/ or exp alcohol drinking/	350072	
13	10 or 11 or 12	835647	SUD indication line for psychotherapy drugs other than ibogaine

14	(demoral* or distress* or stress* or end-of-life or palliative or hopeless* or death or hospice or life-threat* or serious-illness* or end-stage*).ti,ab,kw,kf.	2116065	
15	exp morale/ or exp terminal care/ or existentialism/ or exp stress, psychological/ or palliative care/	252616	
16	14 or 15	2201975	Demoralization indication
17	(methamphetamine* or substance or drug* or polydrug or cocaine or crack or nicotine or tobacco or opioid* or opiate* or psychostimulant* or stimulant* or narcotic* or heroin or amphetamine*).ti,ab,kw,kf. or exp amphetamine/ or exp cocaine/ or exp smoking/ or exp smoking cessation/ or exp nicotine/ or exp Narcotics/ or exp Opiate alkaloids/ or exp central nervous system stimulants/ or exp Amphetamines/	2524267	
18	9 and 17	537381	
19	11 or 12 or 18	871448	Substance use disorders line for ibogaine
20	lysergic acid diethylamide/ or (LSD or 'lysergic acid' or lysergide).ti,ab,kw,kf.	9337	LSD
21	3,4-methylenedioxyamphetamine/ or n-methyl-3,4-methylenedioxyamphetamine/ or (MDMA or methylenedioxymethamphetamine or methylene-dioxymethamphetamine or methylene-dioxy-methamphetamine or midomafetamine).ti,ab,kw,kf.	6060	MDMA
22	psilocybin/ or (psiloc?bin* or psilocin*).ti,ab,kw,kf.	1396	Psilocybin
23	(N-DMT or dimethyltryptamine or dimethyl-tryptamine or ayahuasca or banisteriopsis).ti,ab,kw,kf. or Banisteriopsis/ or exp N,N-dimethyltryptamine/	1618	ayahuasca/DMT
24	exp Ibogaine/ or (ibogain* or noribogain* or nor-ibogain* or iboga or methoxyibogamine or ibogamine or NIH-10567 or Endabuse).ti,ab,kw,kf.	624	ibogaine
25	((randomized controlled trial or controlled clinical trial).pt. or randomi?ed.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (exp animals/ not humans.sh.)	1375664	RCT hedge
26	3 and 20 and 25	88	
27	limit 26 to yr="2010 -Current"	69	LSD anxiety 2010-current
28	7 and 20 and 25	74	
29	limit 28 to yr="2010 -Current"	51	LSD-depression 2010-present
30	4 and 21 and 25	59	
31	limit 30 to yr="2010 -Current"	53	MDMA-PTSD search
32	3 and 21 and 25	92	
33	limit 32 to yr="2010 -Current"	75	MDMA-anxiety RCT search
34	7 and 23 and 25	37	
35	limit 34 to yr="2010 -Current"	34	ayahuasca-depression RCT

36	7 and 22 and 25	79	
37	limit 36 to yr="2010 -Current"	79	Psilocybin-depression RCT search
38	16 and 22 and 25	33	
39	limit 38 to yr="2010 -Current"	33	Psilocybin-demoralization RCT search
40	4 and 22 and 25	12	
41	limit 40 to yr="2010 -Current"	12	Psilocybin-PTSD search
42	13 and 22 and 25	80	
43	limit 42 to yr="2010 -Current"	66	Psilocybin-SUD search
44	19 and 24 and 25	14	
45	limit 44 to yr="2010 -Current"	8	ibogaine-SUD search 2010-present
46	3 and 22 and 25	64	
47	limit 46 to yr="2010 -Current"	61	Psilocybin-anxiety search
48	27 or 29 or 31 or 33 or 35 or 37 or 39 or 41 or 43 or 45 or 47	243	All drug-disease pairs for 2010-present with RCT hedge

Search 2: Embase

Table B2. Embase Search for Experimental Trials for Target Drug-Disease Pairs

Search date: June 6, 2022

#	Search String	Results
1	'anxiety'/exp OR 'anxiety disorder'/exp OR 'mental stress'/exp	653,658
2	anxiet*:ti,ab,kw OR anxious:ti,ab,kw OR ((affective NEXT/1 (symptom* OR disorder*)):ti,ab,kw) OR 'adjustment disorder*':ti,ab,kw OR agoraphobi*:ti,ab,kw OR phobic:ti,ab,kw OR phobia:ti,ab,kw OR panic:ti,ab,kw OR obsessive:ti,ab,kw OR ocd:ti,ab,kw OR stress:ti,ab,kw OR neurosis:ti,ab,kw OR neuroses:ti,ab,kw OR neurotic:ti,ab,kw OR distress:ti,ab,kw OR gad:ti,ab,kw OR psychoneuro*:ti,ab,kw	1,647,673
3	#1 OR #2	1,845,613
4	'posttraumatic stress disorder'/exp OR trauma*:ti,ab,kw OR posttrauma*:ti,ab,kw OR ptsd:ti,ab,kw OR ((stress NEXT/2 (syndrome OR disorder)):ti,ab,kw) OR ptss:ti,ab,kw	602,906
5	'depression'/exp OR 'mood disorder'/de	601,344

6	((affective NEXT/2 (state* OR symptom* OR disorder*)):ti,ab,kw) OR depressed:ti,ab,kw OR depressive*:ti,ab,kw OR depression:ti,ab,kw OR mdd:ti,ab,kw OR trd:ti,ab,kw OR dysthymi*:ti,ab,kw OR (((mood OR mental OR behavior*) NEXT/2 disorder*):ti,ab,kw)	773,214
7	#5 OR #6	962,609
8	methamphetamine*:ti,ab,kw OR substance:ti,ab,kw OR drug*:ti,ab,kw OR polydrug:ti,ab,kw OR cocaine:ti,ab,kw OR crack:ti,ab,kw OR nicotine:ti,ab,kw OR tobacco:ti,ab,kw OR 'amphetamine derivative'/exp OR 'cocaine'/exp OR 'nicotine'/exp OR 'smoking'/exp OR 'smoking cessation'/exp	3,391,899
9	abstin*:ti,ab,kw OR abstain*:ti,ab,kw OR abuse*:ti,ab,kw OR addict*:ti,ab,kw OR dependen*:ti,ab,kw OR misus*:ti,ab,kw OR overdose:ti,ab,kw OR withdrawal*:ti,ab,kw OR disorder*:ti,ab,kw OR cess*:ti,ab,kw	4,317,045
10	#8 AND #9	714,562
11	alcohol*:ti,ab,kw AND (abuse*:ti,ab,kw OR abstin*:ti,ab,kw OR abus*:ti,ab,kw OR addict*:ti,ab,kw OR consum*:ti,ab,kw OR dependen*:ti,ab,kw OR disorder*:ti,ab,kw OR drink*:ti,ab,kw OR excess*:ti,ab,kw OR misus*:ti,ab,kw OR problem*:ti,ab,kw OR risk*:ti,ab,kw OR withdrawal*:ti,ab,kw OR treatment:ti,ab,kw OR cess*:ti,ab,kw)	345,106
12	'drug dependence'/exp OR 'drinking behavior'/exp	317,250
13	#10 OR #11 OR #12	1,105,774
14	demoral*:ti,ab,kw OR distress*:ti,ab,kw OR stress*:ti,ab,kw OR 'end of life':ti,ab,kw OR palliative:ti,ab,kw OR hopeless*:ti,ab,kw OR death:ti,ab,kw OR hospice:ti,ab,kw OR 'life threat*':ti,ab,kw OR 'serious illness*':ti,ab,kw OR 'end stage*':ti,ab,kw	2,867,106
15	'demoralization'/exp OR 'hopelessness'/exp OR 'terminal care'/exp OR 'mental stress'/exp OR 'existentialism'/exp OR 'palliative therapy'/exp	373,071
16	#14 OR #15	3,009,684
17	methamphetamine*:ti,ab,kw OR substance:ti,ab,kw OR drug*:ti,ab,kw OR polydrug:ti,ab,kw OR cocaine:ti,ab,kw OR crack:ti,ab,kw OR nicotine:ti,ab,kw OR tobacco:ti,ab,kw OR opioid*:ti,ab,kw OR opiate*:ti,ab,kw OR psychostimulant*:ti,ab,kw OR stimulant*:ti,ab,kw OR heroin OR amphetamine*:ti,ab,kw OR 'amphetamine derivative'/exp OR 'cocaine'/exp OR 'nicotine'/exp OR 'smoking'/exp OR 'smoking cessation'/exp OR 'narcotic analgesic agent'/exp OR 'narcotic agent'/exp OR 'central stimulant agent'/exp OR 'psychostimulant agent'/exp	4,105,794

18	#9 AND #17	877,003
19	#11 OR #12 OR #18	1,247,598
20	lsd:ti,ab,kw OR 'lysergic acid':ti,ab,kw OR lysergide:ti,ab,kw OR 'lysergide'/exp	15,164
21	'3,4 methylenedioxyamphetamine'/exp OR 'midomafetamine'/exp OR mdma:ti,ab,kw OR methylenedioxymethamphetamine:ti,ab,kw OR 'methylene dioxymethamphetamine':ti,ab,kw OR 'methylene dioxy methamphetamine':ti,ab,kw OR midomafetamine:ti,ab,kw	11,941
22	'psilocybine'/exp OR 'psilocin'/exp OR psiloc*bin*:ti,ab,kw OR psilocin*:ti,ab,kw	2,539
23	'ayahuasca'/exp OR 'n,n dimethyltryptamine'/exp OR 'banisteriopsis'/exp OR 'n dmt':ti,ab,kw OR dimethyltryptamine:ti,ab,kw OR 'dimethyl tryptamine':ti,ab,kw OR ayahuasca:ti,ab,kw OR banisteriopsis:ti,ab,kw	2,055
24	'ibogaine'/exp OR 'ibogamine'/exp OR 'noribogaine'/exp OR ibogaine*:ti,ab,kw OR noribogain*:ti,ab,kw OR 'nor ibogain*':ti,ab,kw OR iboga:ti,ab,kw OR methoxyibogamine:ti,ab,kw OR ibogamine:ti,ab,kw OR 'nih-10567':ti,ab,kw OR endabuse:ti,ab,kw	878
25	'crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR ((cross NEXT/1 over*):de,ab,ti) OR placebo*:de,ab,ti OR ((doubl* NEAR/1 blind*):de,ab,ti) OR ((singl* NEAR/1 blind*):de,ab,ti) OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti	2,943,668
26	#3 AND #20 AND #25	253
27	#3 AND #20 AND #25 AND [2010-2022]/py	199
28	#7 AND #20 AND #25	223
29	#7 AND #20 AND #25 AND [2010-2022]/py	160
30	#4 AND #21 AND #25	122
31	#4 AND #21 AND #25 AND [2010-2022]/py	113
32	#3 AND #21 AND #25	321
33	#3 AND #21 AND #25 AND [2010-2022]/py	248
34	#7 AND #23 AND #25	90

35	#7 AND #23 AND #25 AND [2010-2022]/py	82
36	#7 AND #22 AND #25	226
37	#7 AND #22 AND #25 AND [2010-2022]/py	217
38	#16 AND #22 AND #25	83
39	#16 AND #22 AND #25 AND [2010-2022]/py	79
40	#4 AND #22 AND #25	52
41	#4 AND #22 AND #25 AND [2010-2022]/py	49
42	#13 AND #22 AND #25	181
43	#13 AND #22 AND #25 AND [2010-2022]/py	162
44	#19 AND #24 AND #25	35
45	#19 AND #24 AND #25 AND [2010-2022]/py	25
46	#3 AND #22 AND #25	187
47	#3 AND #22 AND #25 AND [2010-2022]/py	173
48	#27 OR #29 OR #31 OR #33 OR #35 OR #37 OR #39 OR #41 OR #43 OR #45 OR #47	685

APPENDIX C – CITATIONS OF HEALTHY VOLUNTEER CLINICAL TRIALS FOR TARGET PSYCHOTHERAPY DRUGS

3.4 RCTs and SRs conducted with healthy volunteers, by drug, with or without comparator

The following is a list of citations for *possible* clinical trials or systematic reviews (SRs) that included least some healthy volunteers (ie, people without a diagnosed mental health condition that were enrolled in a psychotherapy drug trial that aimed treat that condition) based on information from the title or abstract. Trials exclusively of healthy volunteers were excluded from the annotated bibliography. There are approximately 121 unique citations. Some citations are repeated more than once under different psychotherapy drugs or different comparators if they meet criteria for more than one category. Additionally, some citations overlap with studies included in the annotated bibliography (eg, if they included healthy participants, and people with a diagnosed mental health condition).

3.4.1 Ayahuasca

Clinical trials with comparator

1. de Almeida RN, Galvao ACdM, da Silva FS, et al. Modulation of Serum Brain-Derived Neurotrophic Factor by a Single Dose of Ayahuasca: Observation From a Randomized Controlled Trial. *Frontiers in psychology*. 2019;10:1234.
2. Galvão ACM, de Almeida RN, Silva EAS, et al. Cortisol modulation by ayahuasca in patients with treatment resistant depression and healthy controls. Frontiers in Psychiatry. 2018;9(MAY).
3. Galvão-Coelho NL, de Menezes Galvão AC, de Almeida RN, et al. Changes in inflammatory biomarkers are related to the antidepressant effects of Ayahuasca. *Journal of Psychopharmacology*. 2020;34(10):1125-1133.
4. Hutten N, Mason N, Dolder P, et al. Low doses of lsd acutely increase bdnf blood plasma levels in healthy volunteers: Preliminary findings. *Neuropsychopharmacology*. 2020;45:308-309.
5. Kuypers K, De Sousa Fernandes Perna EB, De Sousa Fernandes P, et al. The novel psychoactive phenetylamine 4-fluoroamphetamine produces a mild psychedelic state without affecting creative thinking. *European Neuropsychopharmacology*. 2019;29:S177-S178.
6. Rocha JM, Rossi GN, de Lima Osorio F, et al. Effects of Ayahuasca on the Recognition of Facial Expressions of Emotions in Naive Healthy Volunteers: A Pilot, Proof-of-Concept, Randomized Controlled Trial. *Journal of clinical psychopharmacology.* 2021;41(3):267-274.
7. Wiesner I, Falchi M, Palhano-Fontes F, Feilding A, Ribeiro S, Tofoli LF. LSD, madness and healing: Mystical experiences as possible link between psychosis model and therapy model. *Psychological medicine*. 2021:1-15.

SRs with comparator

8. Bender D, Hellerstein DJ. Assessing the risk–benefit profile of classical psychedelics: a clinical review of second-wave psychedelic research. *Psychopharmacology*. 2022.
9. Galvao-Coelho NL, Marx W, Gonzalez M, et al. Classic serotonergic psychedelics for mood and depressive symptoms: a meta-analysis of mood disorder patients and healthy participants. *Psychopharmacology*. 2021;238(2):341-354.

10. Morillo CL, Guerrero GP, Martinez ES. P.0321 Ayahuasca as a rescue treatment in depressive patients resistant to pharmacological treatment: a systematic review. *European Neuropsychopharmacology*. 2021;53:S233-S234.
11. Orsolini L, Chiappini S, Papanti D, et al. How does ayahuasca work from a psychiatric perspective? Pros and cons of the entheogenic therapy. *Human Psychopharmacology*. 2020;35(3).
12. Rossi GN, Dias ICDS, Baker G, et al. Ayahuasca, a potentially rapid acting antidepressant: focus on safety and tolerability. *Expert Opinion on Drug Safety*. 2022.

Studies without comparator

n/a

3.4.2 LSD

Clinical trials with comparator

13. Hutten N, Mason N, Dolder P, et al. Low doses of lsd acutely increase bdnf blood plasma levels in healthy volunteers: Preliminary findings. *Neuropsychopharmacology*. 2020;45:308-309.
14. Wiesner I, Falchi M, Palhano-Fontes F, Feilding A, Ribeiro S, Tofoli LF. LSD, madness and healing: Mystical experiences as possible link between psychosis model and therapy model. *Psychological medicine*. 2021:1-15.
15. Bershad A, Schepers S, Bremmer M, de Wit H. Subjective and Behavioral Effects of Microdoses of LSD in Healthy Human Volunteers. *Biological Psychiatry*. 2019;85(10):S345.
16. Bershad A, Van Hedger K, Keedy S, Bremmer M, De Wit H. Individuals with high trait negative emotionality are more sensitive to the subjective effects of a microdose of LSD. *Neuropsychopharmacology*. 2019;44:136-137.
17. Bershad AK, Preller KH, Lee R, et al. Preliminary Report on the Effects of a Low Dose of LSD on Resting-State Amygdala Functional Connectivity. *Biological psychiatry Cognitive neuroscience and neuroimaging*. 2020;5(4):461-467.
18. Bershad AK, Schepers ST, Bremmer MP, Lee R, de Wit H. Acute Subjective and Behavioral Effects of Microdoses of Lysergic Acid Diethylamide in Healthy Human Volunteers. *Biological psychiatry*. 2019;86(10):792-800.
19. Carhart-Harris R. Results: Of a multi-modal neuroimaging study of LSD and a psilocybin for treatment-resistant depression clinical trial. *Neuropsychopharmacology*. 2015;40:S91-S92.
20. Carhart-Harris RL, Kaelen M, Whalley MG, Bolstridge M, Feilding A, Nutt DJ. LSD enhances suggestibility in healthy volunteers. *Psychopharmacology*. 2015;232(4):785-794.
21. De Wit H, Molla H, Bershad A, Bremmer M, Feilding A, Lee R. Repeated microdoses of LSD in healthy adults: A placebo-controlled study. *Neuropsychopharmacology*. 2021;46:511.
22. Dolder PC, Schmid Y, Mueller F, Borgwardt S, Liechti ME. LSD acutely impairs fear recognition and enhances emotional empathy and sociality. *European Neuropsychopharmacology*. 2016;26:S261.
23. Dolder PC, Schmid Y, Mueller F, Borgwardt S, Rentsch KM, Liechti ME. Acute dose-response effects of LSD in healthy humans. *European Neuropsychopharmacology*. 2016;26:S248-S249.
24. Dolder PC, Schmid Y, Muller F, Borgwardt S, Liechti ME. LSD Acutely Impairs Fear Recognition and Enhances Emotional Empathy and Sociality. *Neuropsychopharmacology*. 2016;41(11):2638-2646.

25. Family N, Maillet EL, Williams LTJ, et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of low dose lysergic acid diethylamide (LSD) in healthy older volunteers. *Psychopharmacology*. 2020;237(3):841-853.
26. Holze F, Ley L, Müller F, et al. Direct comparison of the acute effects of lysergic acid diethylamide and psilocybin in a double-blind placebo-controlled study in healthy subjects. *Neuropsychopharmacology*. 2022;47(6):1180-1187.
27. Holze F, Vizeli P, Ley L, et al. Acute dose-dependent effects of lysergic acid diethylamide in a double-blind placebo-controlled study in healthy subjects. *Neuropsychopharmacology*. 2021;46(3):537-544.
28. Holze F, Vizeli P, Muller F, et al. Distinct acute effects of LSD, MDMA, and D-amphetamine in healthy subjects. *Neuropsychopharmacology*. 2020;45(3):462-471.
29. Hutten NRPW, Mason NL, Dolder PC, et al. Mood and cognition after administration of low LSD doses in healthy volunteers: A placebo controlled dose-effect finding study. *European neuropsychopharmacology*. 2020;41:81-91.
30. Kuypers K, Hutten N, Mason N, et al. Creative processes under the influence of a low dose of LSD: A placebo-controlled, double-blind trial in healthy volunteers. *Neuropsychopharmacology*. 2021;46:514.
31. Liechti ME, Holze F, Vizeli P, Schmid Y. Acute effects of LSD in healthy subjects and in patients during LSD-assisted psychotherapy. *Psychotherapy and Psychosomatics*. 2019;88:75.
32. Moujaes F, Rieser N, de Matos NP, et al. P.0833 Neural correlates of pharmacologically and non-pharmacologically induced altered states of consciousness. *European Neuropsychopharmacology*. 2021;53:S608-S609.
33. Muller F, Dolder PC, Schmidt A, Liechti ME, Borgwardt S. Altered network hub connectivity after acute LSD administration. *NeuroImage Clinical*. 2018;18:694-701.
34. Murray CH, Tare I, Perry CM, Malina M, Lee R, de Wit H. Low doses of LSD reduce broadband oscillatory power and modulate event-related potentials in healthy adults. *Psychopharmacology*. 2021.
35. Preller KH, Burt JB, Ji JL, et al. Changes in global and thalamic brain connectivity in LSD-induced altered states of consciousness are attributable to the 5-HT2A receptor. *eLife*. 2018;7.
36. Preller KH, Herdener M, Pokorny T, et al. The role of the serotonin 2A receptor in the fabric and modulation of personal meaning in lysergic acid diethylamide (LSD)-induced states. *European Neuropsychopharmacology*. 2016;26:S299-S300.
37. Ramaekers JG, Hutten N, Mason NL, et al. A low dose of lysergic acid diethylamide decreases pain perception in healthy volunteers. *Journal of psychopharmacology*. 2021;35(4):398-405.
38. Schmidt A, Csomor PA, Bachmann R, Kometer M, Vollenweider FX. Emotional face processing in the 5-HT2A model of altered states of consciousness using event-related potentials. *European Neuropsychopharmacology*. 2010;20:S231.
39. Speth J, Speth C, Kaelen M, et al. Decreased mental time travel to the past correlates with default-mode network disintegration under lysergic acid diethylamide. *Journal of psychopharmacology*. 2016;30(4):344-353.
40. Valle M, Maqueda A, Carlos Bouso J, et al. Naltrexone inhibits the subjective effects of salvinorin-A in humans. *Drug and Alcohol Dependence*. 2015;146:e9.

SRs with comparator

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Clinical trial without comparator

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SR without comparator

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3.4.3 MDMA

Clinical trials with comparator

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SRs with comparator

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Study without comparator

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3.4.4 Psilocybin

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SRs with comparator

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Clinical trials without comparator

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SRs without comparator

139. Johnson MW, Hendricks PS, Barrett FS, Griffiths RR. Classic psychedelics: An integrative review of epidemiology, therapeutics, mystical experience, and brain network function. *Pharmacology and Therapeutics.* 2019;197:83-102.

3.4.5 Ibogaine

Clinical trials with comparator

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SR with comparator

141. Adinoff B, Griffiths R, Hendricks P, et al. A new era of treating substance use disorders with psychedelics. *American Journal on Addictions.* 2019;28(3):162-164.

Studies without comparator

n/a

3.4.6 Multiple agents (ie, more than one psychotherapy drug)

Clinical trials with comparator

142. Hutten N, Mason N, Dolder P, et al. Low doses of lsd acutely increase bdnf blood plasma levels in healthy volunteers: Preliminary findings. *Neuropsychopharmacology*. 2020;45:308-309.

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SRs with comparator

149. Bender D, Hellerstein DJ. Assessing the risk–benefit profile of classical psychedelics: a clinical review of second-wave psychedelic research. *Psychopharmacology*. 2022.
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Without comparator

n/a

APPENDIX D – PRISMA DIAGRAM: SCREENING OF STUDIES

This following diagram (**Figure D1)** shows the flow of our literature search through phases of the screening process, including the number of the articles screened and excluded at each stage.

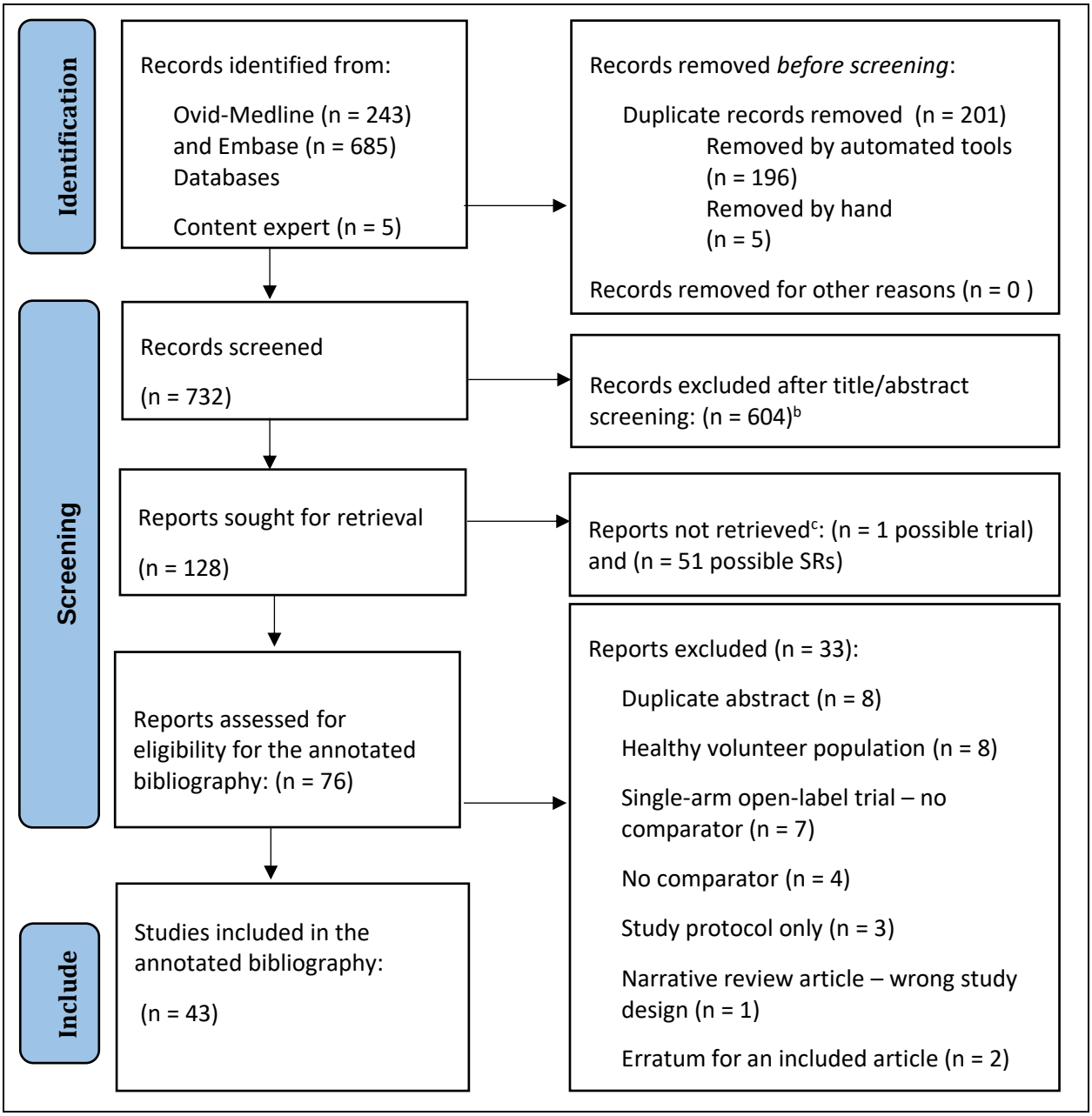

Figure D1. PRISMA Diagram[a]: Identification and Inclusion of Studies for the Annotated Bibliography

Abbreviations: SR, systematic review

Key:

[a] Modified from Page et al. 2021[113]

[b] Some of the articles excluded after screening the title and abstract have been included in **Appendix C** in a list of citations for possible healthy volunteer trials

[c] We did not access one article published in the Dutch language (Strous et al. 2022),[114] but the English abstract includes results from the Carhart-Harris et al. 2021 trial of psilocybin versus escitalopram. The remaining articles were *saved* as possible SRs of RCTs of the target psychotherapy drugs, but it was not feasible to include them in the annotated bibliography.

APPENDIX E – REFERENCES EXCLUDED FROM THE ANNOTATED BIBLIOGRAPHY AFTER FULL TEXT REVIEW, BY REASON FOR EXCLUSION

Duplicate abstract

1. Arnold RM. PC-FACS February 1, 2021. *Journal of Pain and Symptom Management.* 2021;61(4):882-889.
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3. Curran HV, Carhart-Harris R, Nutt D, Ferguson B. Effects of MDMA on self-referent encoding and personal memories: Implications for its use in PTSD. *European Neuropsychopharmacology.* 2015;25:S147.
4. Griffiths R. A single dose of psilocybin produces substantial and enduring decreases in anxiety and depression in patients with a life-threatening cancer diagnosis: A randomized double-blind trial. *Neuropsychopharmacology.* 2015;40:S90-S91.
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Healthy volunteer population

9. Alamia A, Timmermann C, Vanrullen R, Carhart-Harris RL. DMT alters cortical travelling waves. eLife. 2020;9:1-16.
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Single-arm open-label trial (no comparator)

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No comparator

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Study protocol only

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Narrative review article – wrong study design

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This article is published in a Non-English language, so we did not review the full-text. However, based on the abstract, it appears to a summary of the Carhart-Harris et al. 2021 publication.

Erratum for an included article

32. Davis AK, Griffiths RR. Errors in a Response Rate and in Effect Sizes in Study of Psilocybin-Assisted Therapy for Major Depressive Disorder. *JAMA Psychiatry.* 2021;78(5):569.
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